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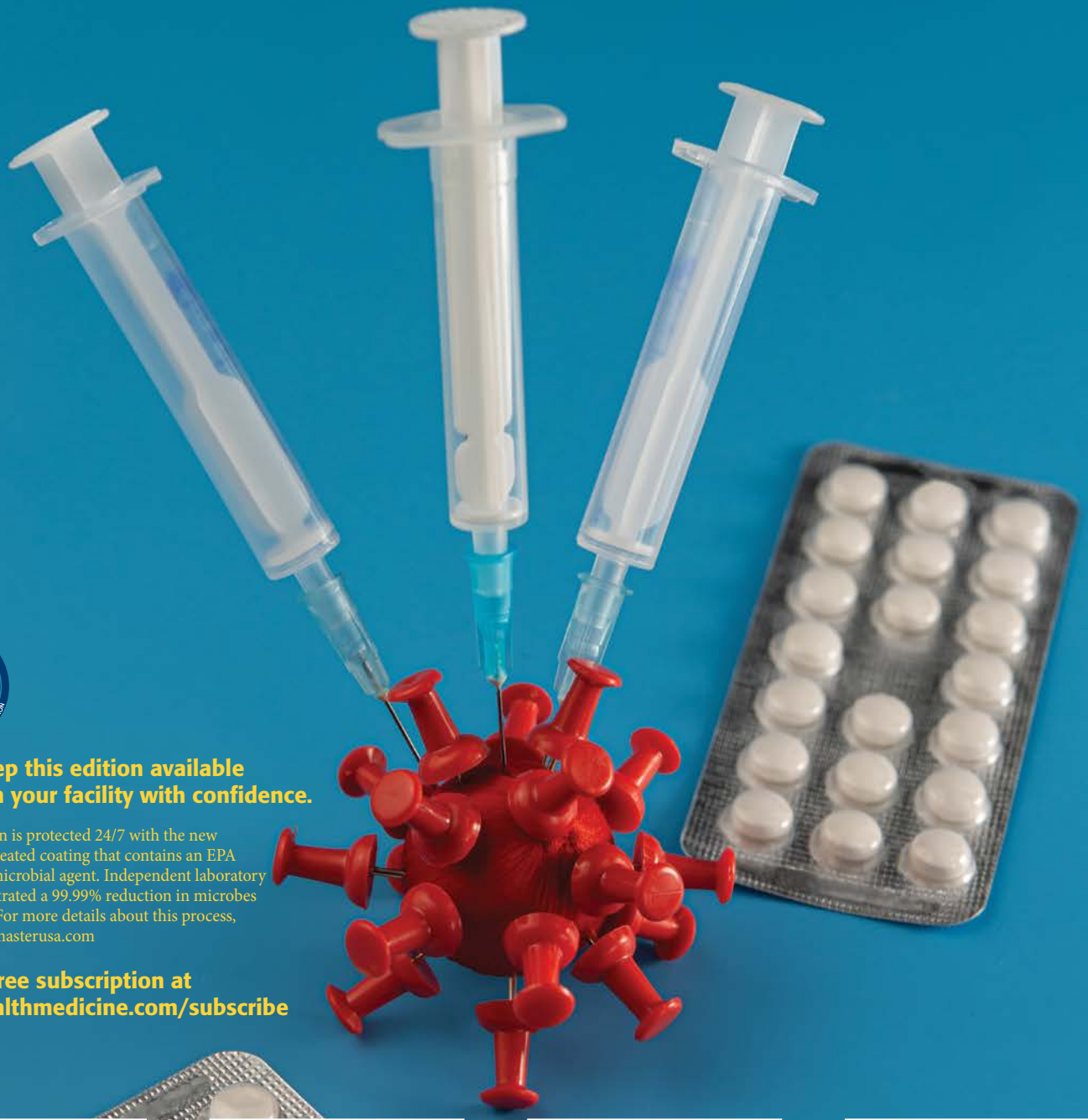

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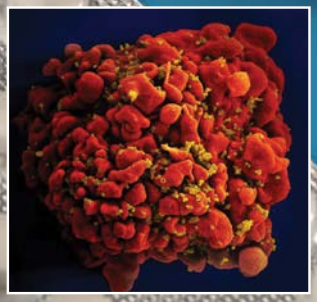

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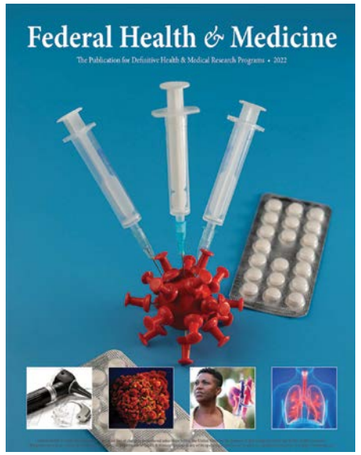

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EXCLUSIVE

Interview with Rebecca G. Baker, PhD about the NIH HEAL Initiative® to Address the Opioid Crisis in the United States

By Tom Adams, Publisher of Federal Health & Medicine

It was my great pleasure to speak with NIH HEAL Initiative Director, Rebecca G. Baker, PhD, about our nation's largest research effort to counter opioid addiction and provide support to the public health professionals serving on the front lines of this crisis in their own communities.

Devastating effects, not only individuals but on their families and communities, has made this research one of the most important efforts of our generation. It must be addressed through team effort, beginning with the awareness and sharing of information that can be used by all communities involved to help those most in need.

Rebecca G. Baker, PhD

Dr. Baker's comments are followed by contact information you can use to learn more about the studies you can participate in with in your own community.

NIH is, the leading public funder of biomedical research. The Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®, is trying to use the power of this research to provide scientific solutions to the opioid crisis of misuse, addiction and overdose, along with helping people safely manage pain.

The HEAL Initiative is helping to end addiction long term by using research to respond to this terrible crisis that has devastated communities across the country. Our most recent data reports that over 100,000 Americans died of a drug overdose within a 12-month period between May 2020 and May 2021. That's a 30 percent increase since COVID-19 started, and it represents the loss of lives who are dear to us, and to our communities.

Overdose deaths are just the tip of the iceberg, there are 10 million Americans who misuse drugs and are at risk for a serious opioid use disorder or overdose. And then we have another 25 million Americans in chronic pain, which is pain they experience every day, and that puts them at risk for opioid abuse from the medication they need to control their pain which has the risk of misuse. HEAL, or "Helping to End Addiction Long-term," was launched in 2018 to address these two criseis together. It crosses all the different parts of NIH, so we have lots of different disease experts within the agency that work as a team. We're really working to pull together all of the scientists and resources that we have across these different institutes, and also working with our partners in the federal government and the private sector to accelerate solutions to these challenges. This has resulted in over 600 different research projects in states across the country with a total research investment of over 2 billion dollars.

There are lots of different types of research that fall within HEAL, all the way from the development of novel medications for pain that do not carry the risk of addiction, and also for patients with opioid use disorder or medications for reversal of overdose to save those lives. Several studies on pain treatment and addiction seeks to take the evidence- based practices that we have and work with communities to help implement them at the local level and that is a really particular innovation with the initiative. You may have heard of "The HEALing Communities Study," which is underway in 67 communities in four states hit really hard with overdoses, working to partner with local community organizations, public health, federal prisons, schools and libraries and everyone they can in the community, testing the impact of community-led sharing of information and resources to prevent overdose deaths.

100 million American adults experience pain and we don't have effective options for all of them, which is really difficult. A primary goal of the initiative is to learn what treatments work best for different pain conditions, because pain associated with arthritis might be treated differently than pain after surgery, or pain from a different chronic condition. Our research is supporting clinical trials for specific interventions for specific pain conditions so that we can share with clinicians the strongest evidence for a treating a particular pain condition. And a lot of it is non-pharmacological; there are really effective mindfulness-based or cognitive behavioral therapies for helping a person manage chronic pain, such as back pain. If the pain doesn't go away, you can try to make it go away with medications or you

can kind of train yourself with effective strategies to cope with the pain. A lot of times that second strategy helps a person function better. You may still experience some pain, but are you able to go to work or care for a family member, are you able to do things that bring joy to your life.

And through our work with patients and people with this experience, we've found that a lot of times those outcomes are actually much more meaningful, depending on how much pain they are experiencing, so we ensure that our treatments and interventions really work for the patient and what matters most to them. This has been a huge source of inspiration for our research. I'll also add that pain is special because it comes alongside a lot of other health needs, so it's rare that a person experiences only pain. A lot of times if it's an older adult or a person with a disability or another chronic health condition, they have a lot of healthcare needs to manage. In addition, the burden of chronic pain doesn't hit everyone equally: our research really needs to address the whole person and also the community in which the person is experiencing pain and receives treatment. That has led us in the past couple of years to focus specifically on some of the ways we can build up equity through our research, and culturally sensitive interventions for specific groups that are especially hard hit by chronic pain and reoccurring health conditions.

This new research aims to address not just a single medical indication or problem, but rather the whole person, their family and their community together.

Another part of the NIH HEAL Initiative addresses the needs of infants and children born to mothers who use drugs during pregnancy. This is a devastating consequence of the opioid crisis. Infants born exposed to opioids during their mother's pregnancy, often undergo withdrawal, meaning they are extremely uncomfortable, and we didn't have a lot of knowledge about the best way to treat them or what the long-term consequence of their drug exposures may be. We have a few different studies underway in that area now, the first is a program we call "ACT NOW."

The Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome Program really seeks to understand what can be done at the time of birth, so it's typical when a baby is born to measure how affected they are. Are they crying for a very long time? Do they have certain symptoms? One of the aspects of this new study is asking some functional questions: are these babies able to be consoled, and are they able to eat and sleep? We call it "eat, sleep, console." This is a non-pharmacological assessment in the hospital after a baby has been born that really promotes time between the mother, the caregiver and the baby. It's extremely popular as you might imagine as an alternative to putting the baby in a position where it's extremely uncomfortable. But there wasn't a lot of evidence around it, so that is one of the first things we started. The study is well underway

now, with the hope that the technique might not only reduce time in the hospital, but also promote moms to help with the baby but also strengthen the relationship with the mother, because we know that is really important for a child's long-term health.

The other question the study is asking is, if an infant is born with withdrawals, then what is the best way to medically treat that withdrawal, could it be giving small amounts of morphine or other medications used to treat opioid disorder like methadone. And we have another study underway to determine what's the best treatment by taking into consideration all of the factors that the baby's mom may have exposed to during her pregnancy. And lastly, we have a really ambitious study called "HEALthy Brain and Child Development Study" (HBCD) that seeks to understand the long- term consequences to those opioid exposures, and how their exposures together with all of the other family's socioeconomic and other environmental exposures contributes to the long-term development of the child.

We have so many different types of studies underway, and we really encourage the participation of our local public health leaders and also folks in the community. We also have certain funding opportunities open that are really directed specifically at local public health officials and groups. If you have activities underway in your community and your would like to collect data about them and maybe use sophisticated tools to analyze the data, then come work with us. We know there are a lot of innovative and creative approaches that communities are taking and they are awesome. These really valuable data are needed by the medical community overall to stem this crisis, but sometimes the manpower or technical power isn't there to serve enough data that everyone can act on. One of the big areas of emphasis now is to expand those connections.

About Dr. Baker:

I was trained as a bench scientist, so I studied how cells in the immune system signal to one another and give information within the body. Following that I started working to help build research programs and coordinate information around different research programs at the NIH, and I worked in a few different areas including the "precision medicine initiative" where all of the programs that seek to gather information from people all across the country to predict what their health outcomes would be and better understand the full picture of a person's health.

Then I worked on the Cancer Moonshot, which was trying to speed the delivery of solutions for treating cancer to patients, so I've worked in a number of areas where lots of different stakeholders come together. When I started working on pain and opioid misuse and addiction it was just such a compelling problem, and compared to some of the other issues I had worked on it just seemed that so much work needed to be done here. There are so many families affected and so many lives cut short, but there isn't necessarily a public appreciation of how important it is to provide evidence-based high-quality care for people with pain and addiction. And there wasn't a perception that this was a challenge for the scientific research community to step up and address, so I was drawn in by the mission and I've been working on it for a couple of years now. I'm really passionate about the needs of the patient and community, and all of the strengths the different players have and how much potential power there is combining those through our initiative.

Additional Resources:

https://heal.nih.gov/research/research-to-practice/healing-communities

https://heal.nih.gov/research/infants-and-children/healthy-brain

About the NIH HEAL Initiative: Research Meets the Moment to Address the Opioid Public Health Crisis

An article published in the *Journal of the American Medical Association* highlights the results of numerous strategies through which the National Institutes of Health's Helping to End Addiction Long-term Initiative, or NIH HEAL Initiative, is finding scientific solutions to address the nation's opioid crisis.

The task is even more urgent since the COVID-19 pandemic fueled a nearly 30% increase in overdose deaths in 2020, the highest 12-month increase in decades. To date, the initiative has funded $1.5 billion to more than 500 research projects to address opioid misuse and pain management.

NIH HEAL Initiative Director Rebecca G. Baker, PhD, National Institute of Neurological Disorders and Stroke Director Walter J. Koroshetz, MD, and National Institute on Drug Abuse Director Nora D. Volkow, MD, describe progress from the initiative's multi-pronged approach that focuses not only on innovative research strategies in both pain and addiction, but also leverages the strengths of communities to address this public health crisis.

These efforts are already yielding results:

- Community-based programs such as the HEALing Communities Study have launched communication campaigns targeting stigma, delivered naloxone widely, and created real-time data dashboards to help guide community decision-making.
- Research has led to a new, non-opioid approach to treat neuropathic pain, currently granted an investigational new drug (IND) application through the U.S. Food and Drug Administration (FDA), and 16 INDs have been approved for existing medications to be tested to treat opioid use disorder.
- Other novel treatments are emerging, such as an oxycodone vaccine that is currently being tested in first-in-human trials.
- New research showcases several innovative devices to treat infants with neonatal opioid withdrawal syndrome or patients with chronic low back pain, reflected by FDA-granted "breakthrough device" status.
- Three large clinical studies are underway toward defining a standard of care for babies born dependent on opioids.

Meeting the moment, the NIH HEAL Initiative is harnessing the power of research to address a public health crisis and is releasing information rapidly.

Findings and publications from initiative-funded studies are part of the HEAL data ecosystem, being built around a cloud-based computing platform that will provide access to the vast array of data generated. These and future research findings will help the millions of individuals, families, and communities affected by poorly treated pain disorders and the opioid crisis.

Article:

Baker, RG; Koroshetz, WJ; Volkow, ND. The Helping to End Addiction Long-term (HEAL) Initiative of the National Institutes of Health

SUBLOCADE® (buprenorphine extended-release) injection, for subcutaneous use (CIII) is indicated for the treatment of moderate to severe opioid use disorder (OUD) in patients who have initiated treatment with a buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days.[1]

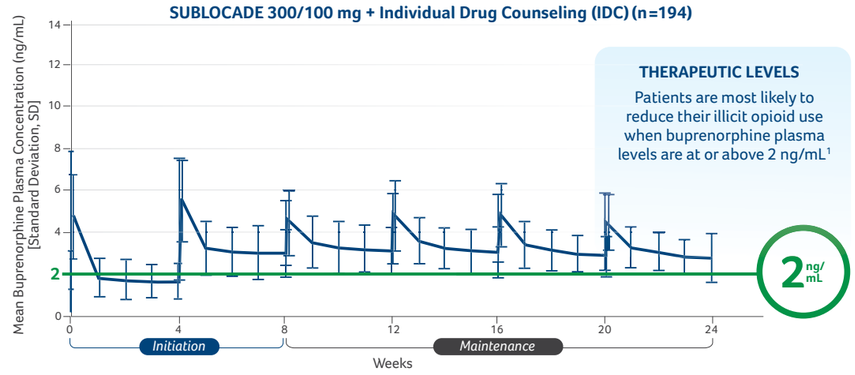
SUBLOCADE should be used as part of a complete treatment plan that includes counseling and psychosocial support.[1]

SUBLOCADE contains buprenorphine, a Schedule III controlled substance that can be abused in a manner similar to other opioids.[1]

All images are not actual patients.

SUBLOCADE® delivers therapeutic levels of buprenorphine so you can be confident it will be there every day between doses[1,4]

Mean Weekly Buprenorphine Plasma Levels Over 24 Weeks (6 Months) of SUBLOCADE Treatment[5,6]



Study Details: Patients with moderate or severe OUD were treated with SUBLOCADE and received 2 monthly injections of 300 mg followed by 4 monthly injections of 100 mg (300/100 mg) or 6 monthly injections of 300 mg (300/300 mg), not shown. Prior to the first dose of SUBLOCADE, treatment was initiated with TM BUP consisting of a 3-day initiation period and up to an 11-day dose stabilization period. The study protocol did not allow for supplemental buprenorphine dosing after starting SUBLOCADE.[4-6]

- Buprenorphine plasma concentrations were assessed before each injection, at 4 hours and 24 hours after injection, and at each weekly visit over the dosing schedule[4]
- Due to inter-patient variability, some patients had occasional concentrations of <2 ng/mL after the second injection and subsequent injections[5]
- Administration of 300/300 mg provided higher buprenorphine concentrations in the range of ~5-10 ng/mL at steady-state (not shown)[4]

DELIVER ON A DIFFERENT LEVEL

Help patients reach and sustain steady therapeutic levels month after month[1,4]

SUMMARY OF IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS HARM OR DEATH WITH INTRAVENOUS ADMINISTRATION; SUBLOCADE RISK EVALUATION AND MITIGATION STRATEGY

- **Serious harm or death could result if administered intravenously. SUBLOCADE forms a solid mass upon contact with body fluids and may cause occlusion, local tissue damage, and thromboembolic events, including life threatening pulmonary emboli, if administered intravenously.**
- **Because of the risk of serious harm or death that could result from intravenous self-administration, SUBLOCADE is only available through a restricted program called the SUBLOCADE REMS Program. Healthcare settings and pharmacies that order and dispense SUBLOCADE must be certified in this program and comply with the REMS requirements.**

Prescription use of this product is limited under the Drug Addiction Treatment Act.

CONTRAINDICATIONS: SUBLOCADE should not be administered to patients who are hypersensitive to buprenorphine or any component of the ATRIGEL® delivery system.

Please see additional Important Safety Information on adjacent pages.

ONCE-MONTHLY
Sublocade®
(buprenorphine extended-release) injection for subcutaneous use CIII
100mg·300mg

WARNINGS AND PRECAUTIONS

Addiction, Abuse, and Misuse: SUBLOCADE contains buprenorphine, a Schedule III controlled substance that can be abused in a manner similar to other opioids. Buprenorphine is sought by people with opioid use disorder and is subject to criminal diversion. Monitor all patients for progression of opioid use disorder and addictive behaviors.

Risk of Life-Threatening Respiratory and Central Nervous System (CNS) Depression: Buprenorphine has been associated with life-threatening respiratory depression and death. Many reports involved misuse by self-injection or concomitant use of buprenorphine and benzodiazepines or other CNS depressants, including alcohol. Use SUBLOCADE with caution in patients with compromised respiratory function. Due to its extended-release characteristics, if SUBLOCADE is discontinued, monitor patients for ongoing buprenorphine effects for several months.

Strongly consider prescribing naloxone at the time SUBLOCADE is initiated or renewed because patients being treated for opioid use disorder have the potential for relapse, putting them at risk for opioid overdose. Educate patients and caregivers on how to recognize respiratory depression and, if naloxone is prescribed, how to treat with naloxone. Emphasize the importance of calling 911 or getting emergency help, even if naloxone is administered.

Please see additional Important Safety Information and BOXED WARNING on adjacent pages.

ONCE-MONTHLY
Sublocade®
(buprenorphine extended-release) injection for subcutaneous use CIII
100mg·300mg

SUMMARY OF IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Opioids can cause sleep-related breathing disorders; e.g., central sleep apnea (CSA), sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. Consider decreasing the opioid using best practices for opioid taper if CSA occurs.

Managing Risks From Concomitant Use of Benzodiazepines or Other CNS Depressants With Buprenorphine: Concomitant use of buprenorphine and benzodiazepines or other CNS depressants increases the risk of adverse reactions including overdose, respiratory depression, and death. Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use with buprenorphine. For patients in buprenorphine treatment, benzodiazepines are not the treatment of choice for anxiety or insomnia.

Risk of Serious Injection Site Reactions: The most common injection site reactions are pain, erythema and pruritus with some involving abscess, ulceration, and necrosis. Some cases resulted in surgical depot removal, debridement, antibiotic administration, and SUBLOCADE discontinuation. The likelihood of serious injection site reactions may increase with inadvertent intramuscular or intradermal administration. Carefully review injection technique to ensure subcutaneous administration. Evaluate and treat serious injection site reactions as appropriate.

Neonatal Opioid Withdrawal Syndrome: Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy. NOWS may be life-threatening if not recognized and treated in the neonate. The risk of NOWS should be balanced against the risk of untreated opioid addiction that is often associated with poor pregnancy outcomes. Advise pregnant women receiving opioid addiction treatment with SUBLOCADE of the risk of neonatal opioid withdrawal syndrome.

Adrenal Insufficiency: Adrenal insufficiency has been reported with opioid use, more often following greater than one month of use.

Risk of Opioid Withdrawal With Abrupt Discontinuation of SUBLOCADE Treatment: If treatment with SUBLOCADE is discontinued, monitor patients for several months for withdrawal and treat appropriately.

Risk of Hepatitis, Hepatic Events: Cases of cytolytic hepatitis and hepatitis with jaundice, ranging from transient asymptomatic elevations in hepatic transaminases to death, have been observed in individuals receiving buprenorphine. Monitor liver function tests prior to treatment and monthly during treatment.

Hypersensitivity Reactions: Hypersensitivity to buprenorphine-containing products have been reported most commonly as rashes, hives, and pruritus. Some cases of bronchospasm, angioneurotic edema, and anaphylactic shock have also been reported.

Precipitation of Opioid Withdrawal in Patients Dependent on Full Agonist Opioids: Buprenorphine may precipitate opioid withdrawal in persons currently physically dependent on full opioid agonists. Verify patients have tolerated and are dose adjusted on transmucosal buprenorphine before subcutaneously injecting SUBLOCADE.

Risks Associated With Treatment of Emergent Acute Pain: When acute pain management or anesthesia are required, treat patients receiving SUBLOCADE currently or within the last 6 months with a non-opioid analgesic whenever possible. If opioid therapy is required, monitor patients closely because higher doses may be required for analgesic effect and therefore, a higher potential for toxicity exists with opioid administration.

Use in Opioid Naïve Patients: SUBLOCADE is not appropriate for use in opioid naïve patients.

Use in Patients With Impaired Hepatic Function: Patients with pre-existing moderate to severe hepatic impairment are not candidates for SUBLOCADE. Patients who develop moderate to severe hepatic impairment on SUBLOCADE should be monitored for several months for toxicity or overdose caused by increased levels of buprenorphine.

Use in Patients at Risk for Arrhythmia: Buprenorphine has been observed to prolong the QTc interval in some patients in clinical trials. Periodic ECG monitoring is recommended if buprenorphine is prescribed to patients with hypokalemia, hypomagnesemia, or clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia. Avoid buprenorphine in patients with a history of Long QT Syndrome or an immediate family member with this condition or those taking Class IA antiarrhythmic medications or Class III antiarrhythmic medications, or other medications that prolong the QT interval.

Impairment of Ability to Drive or Operate Machinery: Caution patients about driving or operating hazardous machinery until they are reasonably certain that SUBLOCADE does not adversely affect their ability to engage in such activities.

Orthostatic Hypotension: Buprenorphine may produce orthostatic hypotension in ambulatory patients.

Elevation of Cerebrospinal Fluid Pressure: Use with caution in patients with head injury, intracranial lesions, and other circumstances when cerebrospinal pressure may be increased.

Elevation of Intracholedochal Pressure: Administer with caution to patients with dysfunction of the biliary tract.

Effects in Acute Abdominal Conditions: Buprenorphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Unintentional Pediatric Exposure: Buprenorphine can cause severe, possibly fatal, respiratory depression in children accidentally exposed to it.

ADVERSE REACTIONS: Adverse reactions commonly associated with SUBLOCADE 300 mg/100 mg and 300 mg/300 mg respectively (≥ 5% subjects) were constipation (9%, 8%), headache (9%, 9%), nausea (9%, 8%), injection site pruritus (6%, 10%), vomiting (9%, 6%), increased hepatic enzymes (5%, 5%), fatigue (4%, 6%), and injection site pain (5%, 6%). Adverse events (AEs) led to premature discontinuation in 4% of the group receiving SUBLOCADE compared with 2% in the placebo group. In the Phase 3 open-label study, AEs leading to drug dose reductions were reported in 7.3% of subjects receiving SUBLOCADE. Dose dependent hepatic effects observed in the Phase 3, double-blind study included the incidence of ALT more than 3 times the upper limit of normal (> 3 x ULN) in 12.4%, 5.4%, and 4.0% of the SUBLOCADE 300/300-mg, SUBLOCADE 300/100-mg, and placebo groups, respectively. The incidence of AST > 3 x ULN was 11.4%, 7.9%, and 1.0%, respectively. Most injection site adverse drug reactions were of mild to moderate severity, with one report of severe injection site pruritus. One injection site ulcer led to study treatment discontinuation.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS (also see Warnings and Precautions): Inhibitors and Inducers of CYP3A4: Monitor patients receiving SUBLOCADE who start or end CYP3A4 inhibitors or inducers for over- or under-dosing.

Antiretrovirals: Non-nucleoside reverse transcriptase inhibitors (NNRTIs): Monitor patients on chronic treatment with SUBLOCADE for increase or decrease in therapeutic effects, if NNRTIs are added to treatment.

Please see additional Important Safety Information and BOXED WARNING on adjacent pages.

Antiretrovirals: Protease inhibitors (PIs): If treatment with atazanavir with and without ritonavir must be initiated in a patient already being treated with SUBLOCADE, monitor for signs and symptoms of over-medication. It may be necessary to remove the depot and treat the patient with a sublingual buprenorphine product that permits rapid dose adjustments.

Antiretrovirals: Nucleoside reverse transcriptase inhibitors (NRTIs): No interactions with buprenorphine and NRTIs are expected.

Serotonergic Drugs: Carefully monitor for serotonin syndrome, particularly during initiation and dose adjustment of serotonergic drug, when SUBLOCADE is used concomitantly with serotonergic drugs.

Monoamine Oxidase Inhibitors (MAOIs): SUBLOCADE is not recommended for patients taking MAOIs or within 14 days of stopping treatment, as MAOIs can increase the effects of buprenorphine.

Muscle Relaxants: Monitor for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of the muscle relaxant as necessary, when SUBLOCADE is used concomitantly with muscle relaxants; strongly consider prescribing naloxone for the emergency treatment of opioid overdose.

Diuretics: Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed, when SUBLOCADE is used concomitantly with diuretics.

Anticholinergic Drugs: Monitor patients for signs of urinary retention or reduced gastric motility when SUBLOCADE is used concomitantly with anticholinergic drugs.

Consult the full Prescribing Information for SUBLOCADE for more information on potentially significant drug interactions.

USE IN SPECIFIC POPULATIONS (also see Warning and Precautions): Pregnancy: The data on use of buprenorphine, the active ingredient in SUBLOCADE, in pregnancy, are limited but do not indicate an increased risk of major malformations specifically due to buprenorphine exposure. Untreated opioid addiction in pregnancy is associated with adverse obstetrical outcomes and often results in continued or relapsing illicit opioid use. Neonatal opioid withdrawal syndrome may occur in newborn infants of mothers who are receiving treatment with SUBLOCADE. Opioid-dependent women on buprenorphine maintenance therapy may require additional analgesia during labor. Use of buprenorphine prior to delivery may result in respiratory depression in the newborn.

Lactation: Studies have demonstrated low levels of buprenorphine in human milk of lactating women receiving buprenorphine and in their infant's urine. The developmental and health benefits of breastfeeding and the mother's clinical need for SUBLOCADE should be considered along with any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition, when prescribing SUBLOCADE to nursing women.

Females and Males of Reproductive Potential: Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

Pediatric Use: The safety and effectiveness of SUBLOCADE have not been established in pediatric populations.

Geriatric Use: Clinical experience with buprenorphine has not identified differences in responses between geriatric and younger patients. Due to possible decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy, geriatric patients taking SUBLOCADE should be monitored for signs and symptoms of toxicity or overdose.

Renal Impairment: No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine.

DRUG ABUSE AND DEPENDENCE: Controlled Substance: SUBLOCADE contains buprenorphine, a Schedule III substance under the Controlled Substances Act.

Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to healthcare providers who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

Abuse: Abuse of buprenorphine poses a risk of overdose and death. Clinical monitoring for evidence of tampering or attempting to remove the depot should be ongoing throughout treatment.

Dependence: Chronic administration of buprenorphine produces physical dependence, characterized by moderate withdrawal signs and symptoms upon abrupt discontinuation. Due to the long-acting nature of SUBLOCADE, withdrawal signs and symptoms may not be evident immediately following the discontinuation of treatment.

OVERDOSAGE: In the event of overdose, the respiratory and cardiac status of the patient should be monitored carefully.

Rx Only.

To report pregnancy or side effects associated with taking SUBLOCADE, please call 1-877-782-6966. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.fda.gov/medwatch or call 1-800-FDA-1088.**

For more information, go to **www.sublocadehcp.com or call 1-877-782-6966. For REMS information visit www.sublocadeREMS.com.**

References: 1. SUBLOCADE [prescribing information]. North Chesterfield, VA: Indivior Inc.; 2021. **2.** The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update [published correction appears in J Addict Med. 2020 May/Jun;14(3): 267]. *J Addict Med.* 2020;14(2S Suppl 1):1-91. doi:10.1097/ADM.0000000000000633 **3.** National Institute on Drug Abuse; 2007. Drugs, Brains, and Behavior: The Science of Addiction. NIH publication 18-DA-5605. https://www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction. Published April 2007. Revised July 2018. Accessed August 30, 2021. **4.** Jones AK, Ngaimisi E, Gopalakrishnan M, Young MA, Laffont CM. Population Pharmacokinetics of a Monthly Buprenorphine Depot Injection for the Treatment of Opioid Use Disorder: A Combined Analysis of Phase II and Phase III Trials. *Clin Pharmacokinet.* 2021;60(4):527-540. doi:10.1007/s40262-020-00957-0 **5.** Haight BR, Learned SM, Laffont CM, et al. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2019;393(10173):778-790. doi:10.1016/S0140-6736(18)32259-1 **6.** Data on file. Indivior Inc. North Chesterfield, VA.

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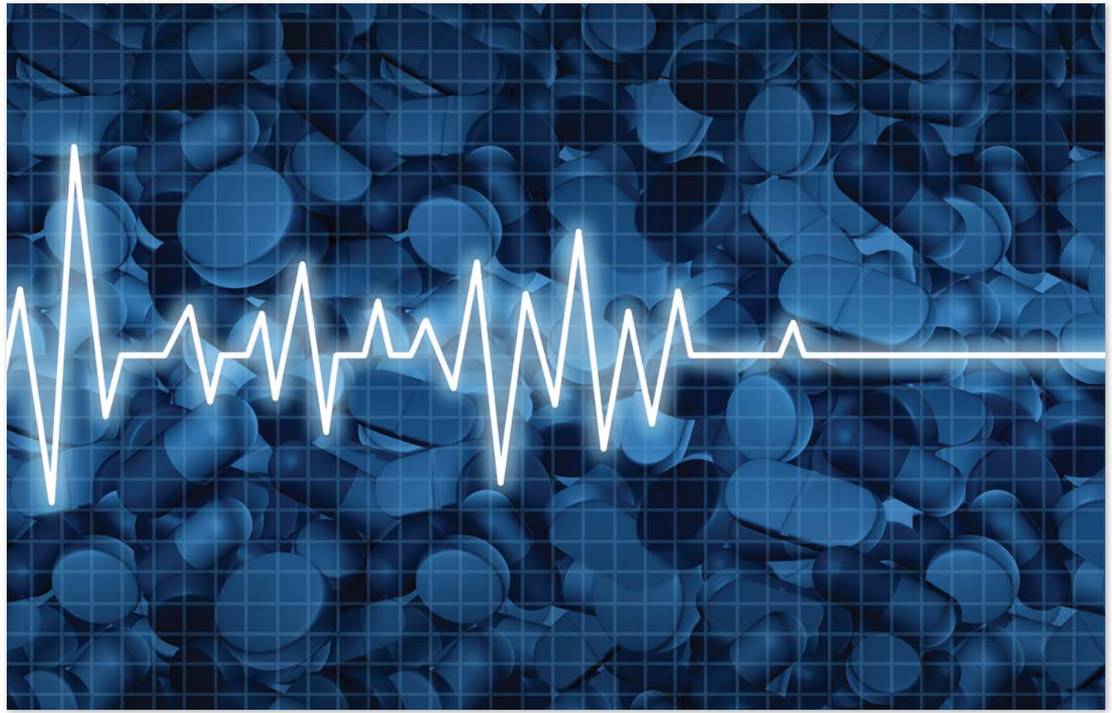
Emergency Department-administered, High-dose Buprenorphine May Enhance Opioid Use Disorder Treatment Outcomes

High-dose buprenorphine therapy, provided under emergency department care, is safe and well tolerated in people with opioid use disorder experiencing opioid withdrawal symptoms, according to a study supported by the National Institutes of Health's National Institute on Drug Abuse (NIDA) through the Helping to End Addiction Long-term Initiative, or the NIH HEAL Initiative.

Lower doses of buprenorphine, a medication approved by the U.S. Food and Drug Administration to treat opioid use disorder, are the current standard of care. However, elevated doses of the medication may provide a critical extended period of withdrawal relief to people after being discharged from the emergency department that may help them navigate barriers to obtaining medications as well as accessing care for the treatment of opioid use disorder. The findings appeared today in JAMA Network Open.

"Emergency departments are at the front lines of treating people with opioid use disorder and helping them overcome barriers to recovery such as withdrawal," said Nora D. Volkow, MD, director of NIDA. "Providing buprenorphine in emergency departments presents an opportunity to expand access to treatment, especially for underserved populations, by supplementing urgent care with a bridge to outpatient services that may ultimately improve long-term outcomes."

Some emergency departments already use higher doses of buprenorphine for the treatment of withdrawal and opioid use disorder in response to the increasing potency of the illicit opioid drug supply and commonly encountered delays in access to follow-up care, but this practice has not been evaluated previously.



Graphic courtesy of NIH

In this study, researchers used a retrospective chart review to analyze data from electronic health records documenting 579 emergency department visits at the Alameda Health System–Highland Hospital in Oakland, California, made by 391 adults with opioid use disorder in 2018. Many of the patients were from vulnerable populations, with 23% experiencing homelessness and 41% having a psychiatric disorder. Most patients were male (68%). Forty-four percent of patients were Black, and 15% were Hispanic or Latino.

The data analysis showed that in 63% of cases, the clinicians administered more than the standard upper limit of 12 mg of sublingual buprenorphine during emergency department induction, and in 23% of cases, patients were given 28 mg or more. Higher doses of buprenorphine were safe and tolerable, and among those given the higher doses, there were no reports of respiratory problems or drowsiness — possible side effects of the medication. The small number of serious adverse events that occurred were determined to be unrelated to high-dose buprenorphine therapy.

Photo by ©iStock.com/SDI Productions

Studies have shown that initiating buprenorphine in emergency departments improves engagement in treatment and is cost effective, but barriers to the medication's use persist. At the time of the study, there were strict controls on buprenorphine prescribing. While clinicians could dispense the medication in the emergency department, only those who had fulfilled the federal certification requirements related to training and ancillary services needed to obtain a buprenorphine prescribing waiver could provide a prescription upon discharge. Patients discharged without a prescription for buprenorphine may experience a return of withdrawal symptoms before they have a chance to access follow-up care. Recent changes to prescribing guidelines by the U.S. Department of Health and Human Services now allow some clinicians treating up to 30 patients to prescribe buprenorphine without the previous training and services criteria.

"Once discharged, many people have difficulty linking to follow-up medical care," said study leader Andrew A. Herring, MD, of Highland Hospital Department of Emergency Medicine. "Adjusting the timing and dosage of buprenorphine in the emergency department, along with resources and counseling aimed at facilitating the transition to outpatient services, may provide the momentum needed to access continuing care."

"This study enhances the evidence we know about emergency-department buprenorphine induction, and could be a gamechanger, particularly for vulnerable populations who would likely benefit from a rapid induction at the time of the visit," says study author Gail D'Onofrio, MD, of Yale University, New Haven, Connecticut, who published the original studies on emergency department-initiated buprenorphine, as well as recent consensus recommendations on the treatment of opioid use disorder in the emergency department.

While the researchers note that their findings need to be prospectively confirmed in other emergency departments, this study suggests that with proper support and training, emergency medicine providers may safely and effectively initiate high-dose buprenorphine therapy.

This work was supported by NIDA's Clinical Trials Network (UG1DA015831), a nationwide consortium aimed at testing drug use interventions and delivering evidence-based therapies to diverse patient populations. Additional support was also provided by the NIH HEAL Initiative.

Reference:

Herring AA, et al. High-dose Buprenorphine Induction for Treatment of Opioid Use Disorder in the Emergency Department. JAMA Network Open. DOI: 10.1001/jamanetworkopen.2021.17128 (2021).

drugabuse.gov

Disparities in Opioid Overdose Deaths Continue to Worsen for Black People, Study Suggests

NIH-supported study underscores the need for racially inclusive approach to address the opioid crisis in hard-hit areas

Non-Hispanic Black individuals in four U.S. states experienced a 38% increase in the rate of opioid overdose deaths from 2018 to 2019, while the rates for other race and ethnicity groups held steady or decreased, according to a new study by the National Institutes of Health published in the American Journal of Public Health. These alarming data are in line with other research documenting a widening of disparities in overdose deaths in Black communities in recent years, largely driven by heroin and illicit fentanyl. The research emphasizes the need for equitable, data-driven, community-based interventions that address these disparities.

The research was conducted as part of the HEALing Communities Study, which aims to significantly reduce opioid-related overdose deaths by helping communities implement evidence-based practices to treat opioid use disorder and reduce other harms associated with opioid use in New York, Massachusetts, Kentucky, and Ohio. It is the largest addiction implementation study ever conducted and is administered in partnership by NIH's National Institute on Drug Abuse (NIDA) and the Substance Abuse and Mental Health Services Administration through the Helping to End Addiction Long-term Initiative, or NIH HEAL Initiative.

"We must explicitly examine and address how structural racism affects health and leads to drug use and overdose deaths," said NIDA Director Nora D. Volkow, MD. "Systemic racism fuels the opioid crisis, just as it contributes mightily to other areas of health disparities and inequity, especially for Black people. We must ensure that evidence-based interventions, tailored to communities, are able to cut through the economic and social factors that drive disparities in substance use and addiction, to reach all people in need of services."

For this study, data were collected from death certificates for 2018 and 2019 across 67 communities with a total population of more than 8.3 million people in the four states participating in the HEALing Communities Study. The researchers calculated rates and trends of opioid overdose deaths overall and for each state, and then further analyzed trends by race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other). Overall, the investigators observed no change in the opioid overdose death rate in these states from 2018 (38.3 deaths per 100,000 people) to 2019 (39.5 deaths per 100,000 people).

However, the researchers observed a 38% overall increase in the opioid overdose death rate for non-Hispanic Black individuals from 2018 to 2019, across these four states. There were no changes overall among the other racial and ethnic groups. Trends varied at the state level and increases among non-Hispanic Black individuals were highest in Kentucky (a 46% increase) and Ohio (a 45% increase). The investigators did not observe a significant increase in Massachusetts among non-Hispanic Black individuals. While opioid overdose death rates were unchanged for non-Hispanic Black individuals in New York, there was an 18% decline among non-Hispanic white individuals, suggesting that non-Hispanic Black individuals have not benefitted equally from prevention and treatment efforts.

Nora D. Volkow, MD, Director of the National Institute on Drug Abuse (NIDA), is senior author of the study. Photo courtesy of NIH

The study authors note that these data add to the evidence of increasing disparities in opioid overdose deaths by race and ethnicity, and highlight the importance of access to timely, local data to inform effective community-tailored strategies to reduce these deaths. Numerous evidence-based prevention and treatment interventions exist for addressing the opioid overdose crisis, overdose education and naloxone distribution, medications for opioid use disorder, behavioral therapies, and recovery support services. Unfortunately, these interventions have largely failed to gain widespread implementation in community settings including addiction treatment, general medical care, social support services, schools, and the justice system.

To address this challenge, the HEALing Communities Study is working with local, state, and federal partners to gain access to data on opioid-related overdose fatalities, treatment, and other related health concerns in a timelier fashion and include important demographic information including race and ethnicity. Early access to these data was instrumental in informing HEALing Communities Study intervention planning, including discussions ensuring evidence-based practices are equitably available to all racial and ethnic groups. For example, these data informed partnerships with Black community organizations to improve access to overdose education and naloxone distribution.

While the data presented here were critical in shaping public health response, the timeliness of data about drug use, addiction, and overdose is an ongoing challenge. National and state data are typically collected annually, access to the data is limited, and data may not be available for months. Health data related to race and ethnicity may be limited or completely unavailable, and mortality data are particularly lagged due to the time required for toxicology testing.

Marc Larochelle, MD, MPH

"The more local and timely data communities have access to, the more tailored their approach can be for interventions," said lead author Marc Larochelle, MD, MPH, a general internal medicine physician at Boston Medical Center and assistant professor of medicine at Boston University School of Medicine. "We know there are disparities in implementation of effective strategies for reducing opioid overdose deaths, but early access to better data like these allows communities to address equity with improved intentionality."

Reference:

MR Larochelle, et al. Disparities in opioid overdose death trends by race/ethnicity, 2018-2019, from the HEALing Communities Study. American Journal of Public Health. DOI: 10.2105/AJPH.2021.306431 (2021).

nida.nih.gov

NIH HEAL INITIATIVE | HEALing Communities Study

Graphic courtesy of NIH

The HEALing Communities Study will test the integration of prevention, overdose treatment, and medication-based treatment in select communities hard hit by the opioid crisis. This comprehensive treatment model will be tested in a coordinated array of settings, including primary care, emergency departments, and other community settings. Findings will establish best practices for integrating prevention and treatment strategies that can be replicated by communities nationwide.

About the Program

NIH and the Substance Abuse and Mental Health Services Administration launched the HEALing Communities Study to investigate how tools for preventing and treating opioid misuse and OUD are most effective at the local level.

This multi-site implementation research study will test the impact of an integrated set of evidence-based practices across health care, behavioral health, justice, and other community-based settings. The goal of the study is to reduce opioid-related overdose deaths by 40 percent over the course of three years. Research sites are partnering with 67 communities highly affected by the opioid crisis in four states, Kentucky, Massachusetts, New York, and Ohio, to measure the impact of these efforts.

The study will also look at the effectiveness of coordinated systems of care designed to increase the number of individuals receiving medication to treat OUD, increase the distribution of naloxone, and reduce high-risk opioid prescribing.

Subscribe to updates from the HEALing Communities Study at https://public.govdelivery.com/accounts/USNIH/subscriber/new?topic_id=USNIH_112

Methamphetamine Overdose Deaths Rise Sharply Nationwide

NIH-supported study finds biggest increase among American Indians and Alaska Natives

Methamphetamine overdose deaths surged in an eight-year period in the United States, according to a study published today in JAMA Psychiatry. The analysis revealed rapid rises across all racial and ethnic groups, but American Indians and Alaska Natives had the highest death rates overall. The research was conducted at the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health.

Deaths involving methamphetamines more than quadrupled among non-Hispanic American Indians and Alaska Natives from 2011-2018 (from 4.5 to 20.9 per 100,000 people) overall, with sharp increases for both men (from 5.6 to 26.4 per 100,000 from 2011-2018) and women (from 3.6 to 15.6 per 100,000 from 2012-2018) in that group. The findings highlight the urgent need to develop culturally tailored, gender-specific prevention and treatment strategies for methamphetamine use disorder to meet the unique needs of those who are most vulnerable to the growing overdose crisis. Long-term decreased access to education, high rates of poverty and discrimination in the delivery of health services are among factors thought to contribute to health disparities for American Indians and Alaska Natives.

"While much attention is focused on the opioid crisis, a methamphetamine crisis has been quietly, but actively, gaining steam — particularly among American Indians and Alaska Natives, who are disproportionately affected by a number of health conditions," said Nora D. Volkow, MD, NIDA director and a senior author of the study. "American Indian and Alaska Native populations experience structural disadvantages but have cultural strengths that can be leveraged to prevent methamphetamine use and improve health outcomes for those living with addiction."

Shared decision-making between patient and health care provider and a holistic approach to wellness are deeply rooted traditions among some American Indian and Alaska Native groups and exist in the Indian health care system. Traditional practices, such as talking circles, in which all members of a group can provide an uninterrupted perspective, and ceremonies, such as smudging, have been integrated into the health practices of many Tribal communities. Leveraging traditions may offer a unique and culturally resonant way to promote resilience to help prevent drug use among young people. Development and implementation of other culturally appropriate and community-based prevention; targeting youth and families with positive early intervention strategies; and provider and community education may also aid prevention efforts among this population.

The study found markedly high death rates among non-Hispanic American Indians and Alaska Natives, as well as a pattern of higher overdose death rates in men compared to women within each racial/ethnic group. However, non-Hispanic American Indian and Alaska Native women had higher rates than non-Hispanic Black, Asian, or Hispanic men during 2012-2018, underscoring the exceptionally high overdose rates in American Indian and Alaska Native populations. The results also revealed that non-Hispanic Blacks had the sharpest increases in overdose death rates during 2011-2018. This represents a worrying trend in a group that had previously experienced very low rates of methamphetamine overdose deaths.

Methamphetamine use is linked to a range of serious health risks, including overdose deaths. Unlike for opioids, there are currently no FDA-approved medications for treating methamphetamine use disorder or reversing overdoses. However, behavioral therapies such as contingency management therapy can be effective in reducing harms associated with use of the drug, and a recent clinical trial reported significant therapeutic benefits with the combination of naltrexone with bupropion in patients with methamphetamine use disorders.

NIDA investigators led by Beth Han, MD, PhD, MPH, obtained data used in the analysis from the 2011-2018 Multiple Cause-of-Death records from the Centers for Disease Control and Prevention's National Vital Statistics System, the nation's most complete database of births and deaths.

Recent national data show that most people who use methamphetamine are between 25 and 54 years old, so the investigators limited their analysis to this age group. When they examined data from this population as a whole, they found a surge in overdose deaths. Deaths involving methamphetamines rose from 1.8 to 10.1 per 100,000 men, and from 0.8 to 4.5 per 100,000 women. This represents a more than five-fold increase from 2011 to 2018.

"Identifying populations that have a higher rate of methamphetamine overdose is a crucial step toward curbing the underlying methamphetamine crisis," said Dr. Han. "By focusing on the unique needs of individuals and developing culturally tailored interventions, we can begin to move away from one-size-fits-all approaches and toward more effective, tailored interventions."

Han B, et al. Methamphetamine overdose deaths in the United States: Sex and racial/ethnic differences. JAMA Psychiatry DOI: 10.1001/jamapsychiatry.2020.4321 (2021).

nida.nih.gov

Expanding Hearing Health Care

Addressing an urgent public health need

"What's that you said?"

Perhaps you've heard yourself say those words more often than you'd like to admit. Or maybe you, a family member, or a friend is consistently turning up the TV volume or can't follow simple conversations in restaurants.

If you are age 70 or older, this is common. Mild-to-moderate hearing loss affects more than 60 percent of 70-year-olds, and more than 80 percent of 80-year-olds have hearing loss, according to NIH's National Institute on Deafness and Other Communication Disorders (NIDCD).

Hearing health care affordability and accessibility is an urgent public health problem. Nearly 37.5 million adults in the U.S. report hearing loss in one or both ears. This number is rising as the number of senior citizens increases.

"Hearing loss is a hidden disability that usually occurs gradually over time, so it's often hard to know how much hearing loss you have or how much you're missing," says Debara Tucci, MD, of Duke University.

James F. Battey, Jr., MD, PhD Photo courtesy of NIH

An NIDCD-funded researcher, Dr. Tucci specializes in ear surgery and health care for people with hearing disorders. She says that if hearing loss is not treated, it can result in serious health, social, and financial problems.

"People with hearing loss have a higher risk of falls, depression, and hospitalization. They also have more difficulties accessing health care," Dr. Tucci says. Hearing loss has also been associated with a higher risk of social withdrawal and dementia in older adults.

Of the millions of adults who could benefit from hearing aids, only 25 percent has actually used one, according to NIDCD.

Social stigma

There are many reasons why people with hearing loss don't use hearing aids. One reason is that there is a stigma associated with them.

"People often see hearing aids as a sign of being old, so they avoid getting the help they need," Dr. Tucci says. Before seeking medical treatment, most hearing aid users have lived with hearing loss for more than 10 years, and their hearing has become worse over time.

Hearing aids, provider visits, and other hearing care treatment can also be very expensive. Medicare and Medicaid offer limited to no coverage for hearing aids, which can cost up to $3,000 per aid.

Affordability and accessibility

Why the high cost? In most cases, the price of the hearing aid includes the services of a hearing health professional.

Currently, if you think you need hearing aids, you must first visit an audiologist or hearing instrument specialist to be tested. You would then purchase the devices from one of these hearing health providers, who would fit you for the hearing aids and adjust them for your needs. They might also counsel you and family members about how to adjust to hearing loss.

Audiologists are health care providers with advanced degrees

who have special training in hearing and balance disorders. Hearing instrument specialists are state-licensed professionals. The requirements vary among states; most states require completing a two-year apprenticeship.

As hearing aids have moved from analog to digital components, the options for different settings have expanded substantially. In addition, the settings on the hearing aids can be adjusted more easily. In some cases, the user can adjust the settings.

Researchers have been exploring why many people don't get the help they need and whether there are ways to ensure that more adults with mild-to-moderate hearing loss get hearing health care.

"The NIDCD has a long history of research and discovery in hearing health," says NIDCD Director James F. Battey, Jr., MD, PhD. "We support studies not only on how we hear, but also on technologies to help people hear better and on delivery models to get hearing loss interventions into the hands of the people who need them."

One study recently found that participants who selected pre-programmed hearing aids using an over-the-counter delivery model reported a similar level of benefit as participants who purchased the same hearing aids through an audiologist following best practices.

The audiology services included fitting the hearing aids and counseling the consumers on how to use them. The study is the first randomized, double-blind, controlled clinical trial to compare the effectiveness of two service-delivery models of hearing aids.

Larry Humes, PhD, professor of speech and hearing sciences at the University of Indiana, is the lead researcher on the study. "I'm excited about the research results," Dr. Humes says. "I'd like more hearing aids to be available to consumers."

On August 18, 2017, a new law was established that will provide more options for some adults with hearing loss. The law gives the Food and Drug Administration (FDA) three years to create standards for safety, effectiveness, and labeling of over-the-counter hearing aids. This new law was a provision in the FDA Reauthorization Act of 2017.

Over-the-counter hearing aids would be FDA-approved for adults with perceived mild-to-moderate hearing loss. Consumers would not need to see licensed hearing professional to purchase certain hearing aids.

Advocates of the law expect the cost of the hearing aids will be much lower than hearing aids sold through current service delivery models.

Image credit Duke University

FDA is developing language to help consumers determine if they are a good candidate for these devices, or if they have symptoms that suggest that they should see a health care professional.

"Over the counter is a good option for people who think they have hearing loss," says Dr. Humes. "It's an affordable way for people to try out the hearing aids at low cost. As their hearing needs become more complex, they may then go to a professional to get more assistance."

Using hearing aids to improve hearing is not as simple as putting on a pair of reading glasses to see better.

"People think they can just use a hearing aid and they will have 20-20 hearing, like they do with eyeglasses," says Dr. Humes. "The problem with older adults and hearing loss is a little more complex."

It takes weeks or months to get used to the louder sound from hearing aids. And treating a hearing problem involves adjustments for the inner ear and the brain. "The convenience of over-the-counter hearing aids is good, but older people must not have expectations that they will hear like a 20-year-old again as soon as they put on their hearing aids," Dr. Humes says.

Adults with perceived mild- to-moderate hearing loss are encouraged to check out low-cost hearing care options when they become available. And, if you are over 65, a visit with an audiologist should be within reach.

"I encourage everyone over age 65 to see their primary care doctor and get a referral to an audiologist for a hearing test, which is covered by Medicare," advises Dr. Tucci. "This is the best way to determine if you have hearing loss and to prevent other health issues related to hearing loss."

medlineplus.gov

Hearing Loss and the Public Health Cycle

The Centers for Disease Control and Prevention's (CDC) work with hearing loss is carried out within a three-stage public health cycle of tracking; research; intervention and prevention; in each of which CDC has been and continues to be a leader. CDC's activities in the area of hearing loss provide a good example of the public health cycle in action.

Tracking

Tracking (also called surveillance) is a powerful tool used to determine who among the general population has a particular condition or disability and how many such individuals are affected. Tracking also is used to find changes among these groups over time. While the findings of the tracking studies that we at CDC conduct often identify research questions to pursue, results from these efforts also can directly inform intervention and prevention strategies. These studies tell CDC who might be more at risk for developing a condition or what might make someone less likely to have it. When we understand who is at risk or what protects someone from a condition, then we have a better idea of what prevention or intervention programs will work. The public health cycle begins again when we use tracking to help us monitor the effects of a particular intervention or prevention program.

In the early 1980s, CDC implemented the first population-based tracking of multiple developmental disabilities (including hearing loss) in the United States — the Metropolitan Atlanta Developmental Disabilities Study (MADDS). MADDS found that approximately 1 of every 1,000 children 10 years of age had a bilateral hearing loss of more than 40 decibels.[1]

By the early 1990s, CDC had built upon the success of MADDS to implement ongoing tracking of selected developmental disabilities. The Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP) continued the work of MADDS in tracking hearing loss, vision loss, cerebral palsy, and intellectual disability. Scientists at CDC recognized the utility of MADDSP in learning the age of first identification among children with hearing loss in an effort to promote the importance of early identification.

MADDSP data from 1991 through 1993 showed that, among children with congenital sensorineural hearing loss, the average age at earliest known diagnosis was 2.9 years; only 8% of those children had their hearing loss diagnosed before they were 1 year of age. Those findings were used to support the initiation of programs and legislation to promote universal newborn hearing screening to assess hearing function of infants before they leave the hospital. Currently, there is extensive evidence supporting the importance of early intervention for children with hearing loss in improving language skills and communication.

Photo courtesy of the CDC

Research

In addition to tracking the prevalence and characteristics of serious hearing loss among school-aged children, we at CDC are able to use MADDSP information to examine potential risk factors for hearing loss and how these factors change over time. For example, improvements in obstetrical and neonatal care have led to higher rates of survival among low birthweight infants in developed countries. MADDSP data have shown an increased risk for hearing loss with lower birthweight. Knowing that low birthweight children are at higher risk for hearing loss has guided researchers to take the next steps to determine if more children are being diagnosed with hearing loss over time and, if so, whether the increase is related to the improved survival rate

Photo courtesy of the CDC

Photo courtesy of the CDC

among low birthweight infants. Knowing about this risk also means that parents and health care providers are more aware of the need to test for hearing problems among low birthweight children.

Intervention and Prevention

MADDSP is the only population-based tracking program for hearing loss in the United States. We are able to use tracking tools, through MADDSP, to measure the effects of prevention and intervention efforts on the prevalence of hearing loss and use of special education services. Early Hearing and Detection Intervention (EHDI) programs promote early infant hearing screening, timely follow-up evaluations, and early intervention services.

Today, newborn hearing screening is conducted in all 50 states, U.S. territories, and the District of Columbia, and over 95% of all newborns are screened. In addition to state efforts, EHDI is supported by a wide range of federal agencies, advocacy groups, professional groups, and the public. Early identification and intervention can help children with hearing loss to maximize their communication and language development.

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Photo courtesy of NIH

Rare Gene Mutation in Some Black Americans May Allow Earlier Screening of Heart Failure

Researchers have linked a rare genetic mutation found mostly in Black Americans and other people of African descent to an earlier onset of heart failure and a higher risk of hospitalization. The findings suggest that earlier screening for the mutation could lead to faster treatment and improved outcomes for heart failure in this vulnerable group, the researchers said. The results of the study, which was largely supported by the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health, appear in the Journal of the American College of Cardiology: Heart Failure.

Photo courtesy of the NIH

"This is the most comprehensive evaluation of the association between this mutation and measures of cardiac structure, heart function, and heart failure risk in an exclusively Black population," said lead study author Ambarish Pandey, MD, assistant professor of internal medicine in the Division of Cardiology at University of Texas Southwestern Medical Center in Dallas. "The results also highlight the importance of early genetic screening in patients at higher risk for carrying the mutation."

Heart failure is a chronic, debilitating condition that develops when the heart can't pump enough blood to meet the body's needs. Despite the name, it does not mean that the heart has stopped beating. Common symptoms include shortness of breath during daily activities or trouble breathing when lying down. The condition affects about 6.5 million people in the United States alone. Black Americans are at higher risk for the condition than any other racial/ethnic group in the U.S., and they experience worse outcomes.

The genetic variant studied in the current research had long ago been linked to a higher risk of heart failure in people of African ancestry. Known as TTR V142I, the gene can cause a condition called transthyretin amyloid cardiomyopathy, which is potentially fatal because protein builds up inside the heart. However, little was known about the impact of the mutation on important clinical-related factors such as heart structure, heart function, hospitalization rates, and blood biomarkers.

To learn more, the researchers studied TTR V142I in a group of middle-aged participants from the 20-year-long Jackson Heart Study, the largest and longest investigation of cardiovascular disease in Black Americans. Of the 2,960 participants selected from the study, about 119 (4%) had the genetic mutation, but none had heart failure at the start. The researchers followed the participants for about 12 years between 2005 and 2016.

During the study period, the researchers observed 258 heart failure events. They found that patients who carried the genetic mutation were at significantly higher risk of developing heart failure, compared to those without the mutation. These patients also developed heart failure nearly four years earlier and had a higher number of heart failure hospitalizations. Researchers said they found no significant difference in death rates between the two groups during this study period.

During follow-up studies, however, they observed significant increases in blood levels of troponin, a protein complex that is an important marker of heart damage, among carriers of the genetic mutation. They did not see any significant associations between the genetic mutation and changes in heart structure and function as evaluated by echocardiographic and cardiac MRI assessments.

"What that means is that the gene is causing heart damage slowly over time," said Amanda C. Coniglio, MD, the lead author of the study and a physician with Duke University School of Medicine in Durham, North Carolina. "The changes are subtle but significant."

UT Southwestern cardiologist Dr. Ambarish Pandey is named a Texas Health Resources Clinical Scholar. Photo courtesy of UT Southwestern

The researchers noted that more studies will be needed to continue assessing participants' heart structure and function and to see, long-term, if increased hospitalization risk translates into higher risk of death.

"Identification of genetic susceptibility to amyloid cardiomyopathy is an important advance related to heart failure, especially given its disproportionate effect on older and multiethnic populations," said Patrice Desvigne-Nickens, MD, a medical officer in the Heart Failure and Arrhythmia Branch in NHLBI's Division of Cardiovascular Sciences.

Adolfo Correa, MD, PhD, study co-author and former director of the Jackson Heart Study, agreed. "About half of Black American men and women living in the United States today have some form of cardiovascular disease, but the root causes are poorly understood," he said. "This study brings us a step closer to better understanding this particular form of gene-related heart failure, as well as the life-saving importance of early screening."

The Jackson Heart Study is supported and conducted in collaboration with Jackson State University (HHSN268201800013I), Tougaloo College (HHSN268201800014I), the Mississippi State Department of Health (HHSN268201800015I/HHSN26800001) and the University of Mississippi Medical Center (HHSN268201800010I, HHSN268201800011I, and HHSN268201800012I) contracts from the NHLBI and the National Institute on Minority Health and Health Disparities. Additional NIH funding support includes the National Institute of Diabetes and Digestive and Kidney Diseases grant 1K08DK099415- 01A1; National Institute of General Medical Sciences grants P20GM104357 and 5U54GM115428.

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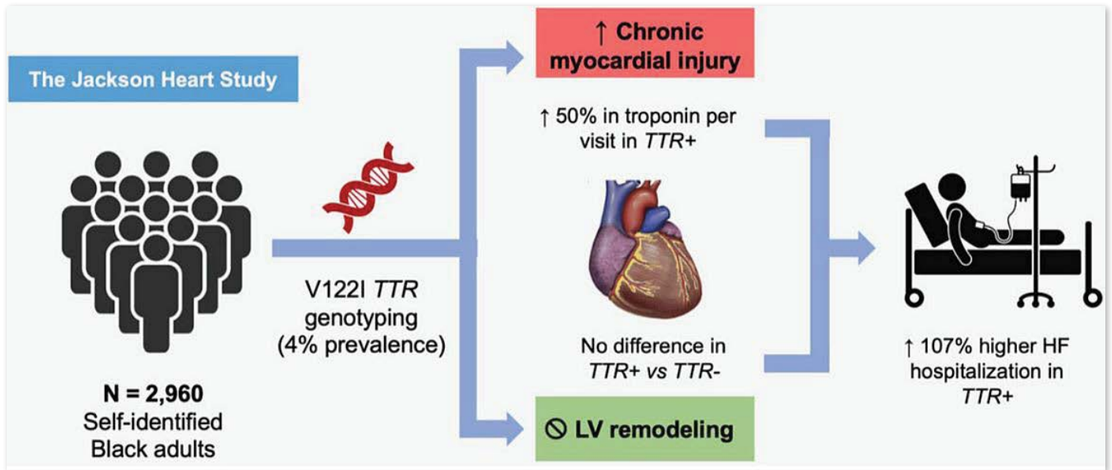

Illustration shows that the V142I variant carrier status was associated with greater downstream burden of chronic myocardial injury, higher risk of heart failure hospitalization, and lower survival-free heart failure. Coniglio, A.C. et al. JACC: Heart Failure

When is the Best Time to Get a Coronary Artery Calcium Scan?

Medical decisions about screening younger adults for a hardening of their arteries, an indicator for heart disease, have often varied. Now, an NHLBI-supported study in the Journal of the American College of Cardiology suggests timelines for coronary artery calcium scans based on a review of 22,346 young to middle-aged adults.

The study's researchers recommend men with diabetes receive these types of cardiac scans, which help identify the earliest formation of plaque that can block blood flow or rupture, at age 37. For women with diabetes, the ideal age is 50. For adults without known risks for premature heart disease, the authors say an ideal time is age 42 for men and 58 for women.

To create these recommendations, researchers partnered with adults who had a significant family history of heart disease or other cardiovascular disease risk factors. Based on these and other imaging exams, researchers found that about one-third of adults in the study had early signs of coronary artery calcification. Upon further review, they found adults with diabetes started accumulating calcium deposits in their coronary arteries six years earlier than adults without diabetes. Adults who smoked, had high blood pressure or high cholesterol, or who had a family history of heart disease started showing signs of calcium accumulation three to four years in advance.

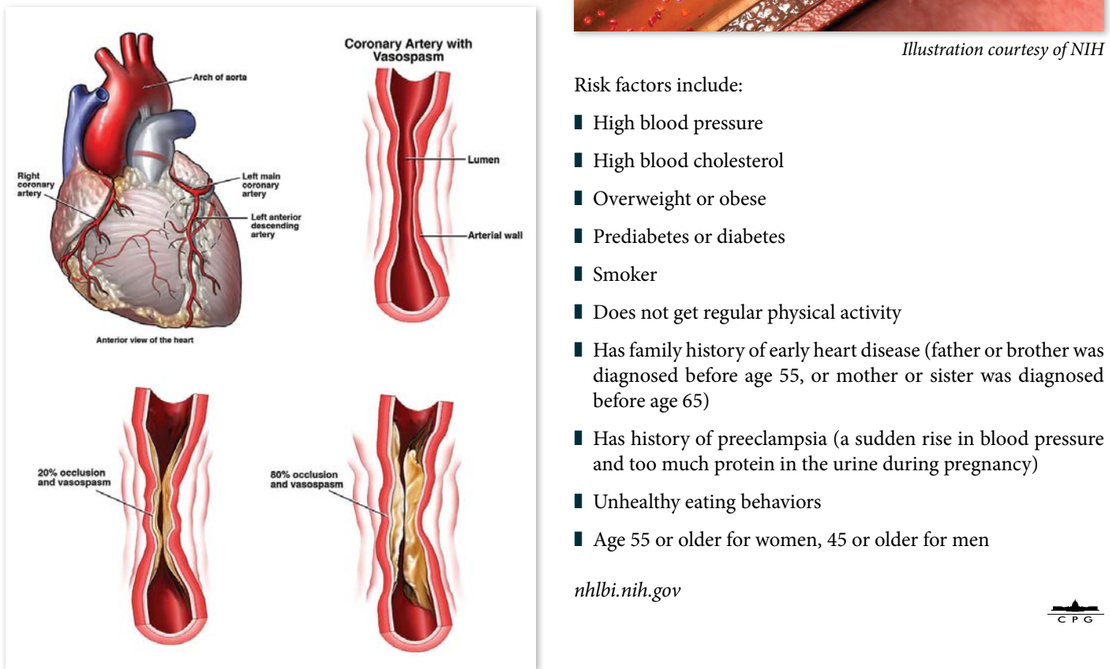

Illustration courtesy of NIH

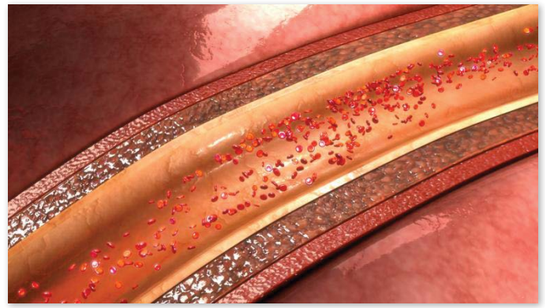

Illustration courtesy of NIH

Risk factors include:

- High blood pressure
- High blood cholesterol
- Overweight or obese
- Prediabetes or diabetes
- Smoker
- Does not get regular physical activity
- Has family history of early heart disease (father or brother was diagnosed before age 55, or mother or sister was diagnosed before age 65)
- Has history of preeclampsia (a sudden rise in blood pressure and too much protein in the urine during pregnancy)
- Unhealthy eating behaviors
- Age 55 or older for women, 45 or older for men

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An Ancient Part of the Immune System Could Advance Heart Disease Research

A cell-based look at how the body responds to immune threats may one day help researchers find better treatments for this major U.S. killer

For more than a decade, researchers have known that a core component of human immune function — called complement — can influence how the body responds to immune threats. Now researchers from the NIH and around the world say they've gained new knowledge about how the body responds to these threats inside of cells, too. They specifically found that complement can activate pro-inflammatory responses, such as cholesterol crystals that can start accumulating within cells.

Since cholesterol buildup and inflammation are known risk factors for heart disease, understanding this intracellular system better may help researchers develop future treatments for cardiovascular disease, the number one killer in the U.S., explains Claudia Kemper, PhD, a senior investigator in the Division of Intramural Research at NHLBI. In fact, adds Kemper, who also leads the Laboratory for Complement and Inflammation Research, part of the scientific team who made this discovery, "it may be the birth of a new area for complement activities."

Kemper shares insight about this field and these findings, which published today in Science Immunology.

First, what is complement?

Complement is an evolutionary old part of our immune system. It is mostly generated by the liver and circulates in blood as a protein system that can detect and remove pathogens, infected or dying cells, and malignantly transformed cells, which can lead to cancer.

Normally, the complement system — which serves as an internal alarm or immune guard — protects us. However, under certain circumstances, the system can malfunction and turn against the host. When that happens, the malfunction can set off or worsen a broad range of inflammatory and autoimmune conditions, including arthritis and atherosclerosis.

What did researchers find that is new in this study?

Researchers knew that in the majority of human diseases, an overactive or underactive complement system is involved on some level. Previously, researchers thought complement operated exclusively in the blood and extracellular space. But earlier work from our Kemper laboratory had shown, surprisingly, that complement can be activated and operate inside of cells. We call this system the "complosome." What was not clear is how it exerts its function.

In this study, we found that complement proteins can directly modulate the activity of mitochondria, the cell's energy power houses, in macrophages — a central type of immune cell.

Under normal circumstances, complement contributes to well-functioning macrophage activity. However, in individuals that choose a very high-fat diet, this internal complement "guard" — we like to call it the mitochondrial-complement axis — first senses an increased, sustained lipid environment within macrophages. Then, it triggers an unwanted chronic inflammatory state in these cells. This process ultimately drives atherosclerosis and cardiovascular disease.

How might these findings change the field of immunology and cardiovascular research?

The "complosome" as a concept is about 10 years old, but it's gaining traction. Publications about this topic are increasing. So far, the complosome can be found in just about all cells researchers have studied — not just immune cells.

However, we have only scratched the surface of complosome biology, and currently we have more questions than answers when it comes to its functions in health and disease. What is becoming clear is that targeting the extracellular complement system may not be sufficient to help prevent atherosclerosis — and that we may need to target the intracellular system as well.

Could researchers use these findings in personalized therapeutics to help people who have coronary artery disease or related conditions?

We really need to learn more about this type of intracellular communication first before we can think about how we may be able to modulate it to help treat disease. So, I think what you are seeing here is maybe the birth of a new area. It's a worthy target. But we are far away from being able to target it successfully in a controlled manner. Still, it is exciting that this new knowledge may enable us to potentially find new therapeutics against one of the biggest killers in our Western world: cardiovascular disease.

Understanding the intracellular functions of complement, the complosome, is a team effort and came as a result of research conducted at NHLBI and other NIH research institutions, and with scientists throughout the world. We hope that our work inspires other groups, both here at the NIH and beyond, to think along the same lines and join us in these research efforts.

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Diverse Genome Sequences Provide a Powerful Tool for Studying Risk of Heart Disease

Study of millions of people from diverse ancestral groups substantially improves identification of genomic variants associated with blood lipid levels

In a large-scale study of people from diverse ancestries, researchers narrowed down the number of genomic variants that are strongly associated with blood lipid levels and generated a polygenic risk score to predict elevated low-density lipoprotein cholesterol levels, a major risk factor for heart disease. The study, published in the journal Nature, was led by the Global Lipids Genetics Consortium. The authors include researchers at the National Human Genome Research Institute (NHGRI), part of the National Institutes of Health.

Lipids are fat-like substances that can be found in blood and body tissues. They come in two major forms — cholesterol and triglycerides. Humans need a certain amount of lipids in the body for normal function, but elevated lipid levels may increase the risk of developing a heart condition. Polygenic risk scores provide an estimate of an individual's risk for specific diseases, based on their DNA changes related to those diseases.

"Finding the set of genomic variants that are important for this trait is key for us to understand the biology and identify new drug targets," said Cristen Willer, PhD, senior author and professor of human genetics at the University of Michigan, Ann Arbor. "These genomic variants then inform how well polygenic risk scores work to determine risk for such diseases."

Since the field's inception, the genomics community has performed over 6,000 studies looking at the association of specific genomic variants and cardiovascular disease. However, the design of these studies overwhelmingly included

Photo credit Harry Wedel, NHGRI

individuals from European ancestral populations.

To address this issue, researchers accumulated data from 201 previous genome-wide association studies, including about 1.65 million individuals from five ancestral groups: African, East Asian, European, Hispanic and South Asian. About 1.32 million of those studies were from European ancestry, and the remaining 350,000 were non-European. The studies contained data on blood levels of the different classes of cholesterol and triglycerides.

The research group calculated the polygenic risk scores using data from each of the different ancestral groups, either separately or all together. Then, they tested the risk scores in a diverse set of studies, including Africans enrolled from Ghana, Kenya and Nigeria as part of the Africa America Diabetes Mellitus study. Charles Rotimi, PhD, scientific director of the NHGRI Intramural Research Program, was the principal investigator of the study.

The results showed a polygenic risk score that includes diverse genomic data is much more predictive of whether a person of any ancestry will have elevated low-density lipoprotein cholesterol levels than a score that only includes European genomic data.

"The message couldn't be more clear. To have a fuller understanding of the effects of genomic variation on disease, we simply must include as many diverse groups of people as possible," said Rotimi, a co-author on the paper. "It is the single biggest way by which we can ensure that the gains of genomic medicine and technologies are equitably deployed to serve the health needs of all human populations."

For each ancestral group, the polygenic risk score that used data from all ancestries worked at least as well as or better than the risk scores derived from data from the same ancestral group.

"These results show that our concerted effort to include many diverse groups of people in genomic research will yield benefits such as new therapeutics and prevention strategies that improve the health of all people," says Cashell Jaquish, PhD, a genetic epidemiologist and program officer within the Division of Cardiovascular Sciences at the National Heart Lung, and Blood Institute.

Funding for the study was provided by the National Heart, Lung and Blood Institute, part of the National Institutes of Health.

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A High-fiber Diet May Improve the Response of Melanoma Patients to Immunotherapy

A diet rich in fiber may help some people being treated for melanoma respond to immunotherapy treatment by influencing the gut microbiome, according to a new study led by researchers at the Center for Cancer Research at the National Cancer Institute (NCI), part of the National Institutes of Health, and the University of Texas MD Anderson Cancer Center. Results from the study, which analyzed both people with melanoma and mouse models of the disease, appear in Science.

Among patients with advanced melanoma who underwent immunotherapy with immune checkpoint blockers, those who consumed at least 20 grams a day of dietary fiber survived the longest without their disease progressing. In contrast, use of probiotic supplements appeared to lessen somewhat the effectiveness of immune checkpoint blocker regimens. Probiotics are live microorganisms typically consumed as a supplement to improve gut health.

"The data suggest that one can target the composition of the gut microbiota and affect the ability of the patient to respond to immunotherapy," said Giorgio Trinchieri, MD, chief of the Laboratory of Integrative Cancer Immunology in NCI's Center for Cancer Research, one of the study's coleaders. "Consuming a diet rich in fiber, like fruits, vegetables, and legumes, could improve your ability to respond to immunotherapy."

Immunotherapy with immune checkpoint blockers helps restore the immune system's natural ability to recognize and kill tumor cells. These drugs have been transformative in melanoma, improving how long some people with advanced disease live, sometimes by years. However, for many patients, immune checkpoint blockers fail to stop their tumors from growing. Several studies have suggested that the composition of the bacteria in the gut may influence the response to immunotherapy.

"The question is, can we change the composition of the type of bacteria in the gut and improve the ability of the patient to respond?" Dr. Trinchieri said.

In a previous study, Dr. Trinchieri and a different group of collaborators showed that some people with melanoma who initially did not respond to treatment with an immune checkpoint blocker did respond after receiving a fecal transplant from a patient who had responded to the drug. The fecal transplant, they concluded, had introduced different gut bacteria that helped make it easier for immune cells to invade and kill their tumors.

"Dietary fiber intake and use of probiotic supplements have also been shown to affect the composition of gut bacteria. More cancer patients are taking probiotic supplements in an effort to improve their gut health, but little is known about how probiotics — which basically change the ecology of the gut bacteria — impact immunotherapy response," he said.

The connection between fiber intake and immunotherapy response has also been unclear. However, a recent study led by Romina Goldszmid, PhD, also of NCI's Center for Cancer Research, showed that mice fed a diet rich in pectin, which is a fiber abundant in apples, were able to stave off tumor growth by activating immune cells and reprogramming the tumor microenvironment.

Giorgio Trinchieri, MD, chief of the Laboratory of Integrative Cancer Immunology in NCI's Center for Cancer Research. Photo credit International Cytokine & Interferon Society

In the new study, Dr. Trinchieri and study co-leads Carrie R. Daniel, PhD, MPH, and Jennifer A. Wargo, MD, of the University of Texas MD Anderson Cancer Center, and their collaborators looked at the composition of fecal microorganisms (the gut microbiota), dietary habits, and probiotic supplement use among patients who were being treated for advanced melanoma with immune checkpoint blockers.

Among the 128 patients whose dietary fiber intake was known, those who reported consuming at least 20 grams of dietary fiber per day (an amount the researchers designated as "sufficient" for the purposes of this study) lived longer without their cancer progressing than those who consumed less dietary fiber. Every 5-gram increase in daily dietary fiber intake corresponded to a 30% lower risk of progression of the disease.

The researchers also looked at the impact of dietary fiber on the response to treatment with anti-PD-1 drugs, a category of immune checkpoint blockers, in mouse models of melanoma.

To mimic the different diets in the melanoma patients, they fed mice either a fiber-rich or a low-fiber diet, injected the mice with melanoma cells, and then treated the mice with anti-PD-1 therapy. Mice given the fiber-rich diet had delayed tumor growth after anti-PD-1 treatment, compared with mice given the low-fiber diet.

The researchers then repeated the experiments in germ-free mice — that is, mice that have no bacteria in their guts.

"In germ-free mice, the diet made no difference in the immunotherapy response," Dr. Trinchieri said. "That suggests that the diet is affecting the response to immune checkpoint therapy by changing the composition of the gut microbiota."

Dr. Trinchieri noted that one possible mechanism through which dietary fiber exerts its beneficial effect is by increasing the types of bacteria in the gut, such as Ruminococcaceae, that produce high levels of certain short-chain fatty acids that have an antitumor effect.

"We did see an increase in one of these short-chain fatty acids, propionate, in mice that were fed a high-fiber diet," Dr. Trinchieri said. "Moreover, patients whose cancer responded to immunotherapy had a greater abundance of Ruminococcaceae bacteria in their gut microbiota compared with those who did not respond to therapy."

Photo credit NIH

The researchers also looked at the impact of probiotics on gut bacteria in the mouse model of melanoma. Mice fed probiotics had a reduced response to treatment with anti-PD-L1 drugs and developed larger tumors than control mice. Further analysis showed that mice fed probiotics had lower levels of tumor-killing immune cells, suggesting a weakened immune response.

A diet rich in fiber may help some people being treated for melanoma respond to immunotherapy treatment by influencing the gut microbiome.

In the human study, nearly one-third of the patients reported they had taken a probiotic supplement within the past month. Although the researchers noted that the small sample size and variety of probiotics used by the patients made it difficult to draw definitive conclusions about the association between probiotic use and response to immune checkpoint blockers, they did observe that patients who consumed the highest levels of dietary fiber with no probiotic use survived the longest.

"The impact of dietary fiber and probiotics on the gut microbiota is only part of the bigger picture," Dr. Trinchieri cautioned. "Many factors can affect the ability of a patient with melanoma to respond to immunotherapy. However, from these data, the microbiota seems to be one of the dominant factors.

The data also suggest that it's probably better for people with cancer receiving immunotherapy not to use commercially available probiotics."

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Fecal Microbiota Transplants Help Patients with Advanced Melanoma Respond to Immunotherapy

For patients with cancers that do not respond to immunotherapy drugs, adjusting the composition of microorganisms in the intestines — known as the gut microbiome — through the use of stool, or fecal, transplants may help some of these individuals respond to the immunotherapy drugs, a new study suggests.

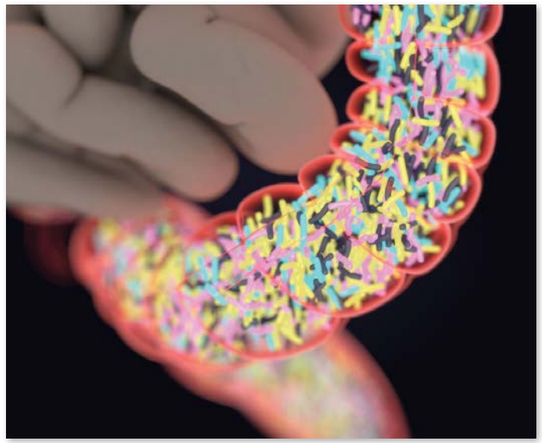
Researchers at the National Cancer Institute (NCI) Center for Cancer Research, part of the National Institutes of Health, conducted the study in collaboration with investigators from UPMC Hillman Cancer Center at the University of Pittsburgh.

In the study, some patients with advanced melanoma who initially did not respond to treatment with an immune checkpoint inhibitor, a type of immunotherapy, did respond to the drug after receiving a transplant of fecal microbiota from a patient who had responded to the drug. The results suggest that introducing certain fecal microorganisms into a patient's colon may help the patient respond to drugs that enhance the immune system's ability to recognize and kill tumor cells. The findings appeared in Science on February 4, 2021.

"In recent years, immunotherapy drugs called PD-1 and PD-L1 inhibitors have benefited many patients with certain types of cancer, but we need new strategies to help patients whose cancers do not respond," said study co-leader Giorgio Trinchieri, MD, chief of the Laboratory of Integrative Cancer Immunology in NCI's Center for Cancer Research. "Our study is one of the first to demonstrate in patients that altering the composition of the gut microbiome can improve the response to immunotherapy. The data provide proof of concept that the gut microbiome can be a therapeutic target in cancer."

More research is needed, Dr. Trinchieri added, to identify the specific microorganisms that are critical for overcoming a tumor's resistance to immunotherapy drugs and to investigate the biological mechanisms involved.

Research suggests that communities of bacteria and viruses in the intestines can affect the immune system and its response to chemotherapy and immunotherapy. For example, previous studies have shown that tumor-bearing mice that do not respond to immunotherapy drugs can start to respond if they receive certain gut microorganisms from mice that responded to the drugs.



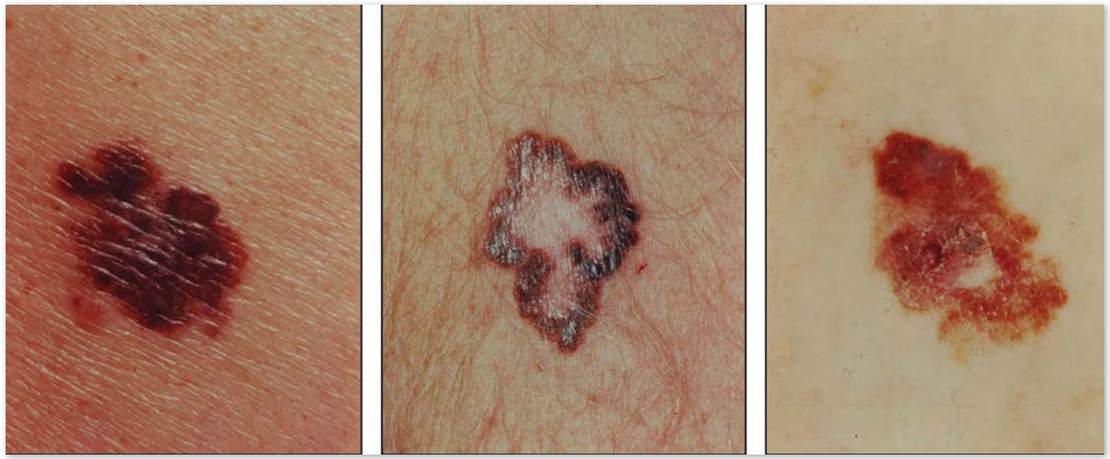
Introducing certain fecal microorganisms into a patient's colon may help the patient respond to immunotherapy drugs. Photo credit NCI and iStock

Changing the gut microbiome may "reprogram" the microenvironments of tumors that resist immunotherapy drugs, making them more favorable to treatment with these medicines, noted Dr. Trinchieri.

To test whether fecal transplants are safe and may help patients with cancer better respond to immunotherapy, Dr. Trinchieri and his colleagues developed a small, single-arm clinical trial for patients with advanced melanoma.

The patients' tumors had not responded to one or more rounds of treatment with the immune checkpoint inhibitors pembrolizumab (Keytruda) or nivolumab (Opdivo), which were administered alone or in combination with other drugs. Immune checkpoint inhibitors release a brake that keeps the immune system from attacking tumor cells.

In the study, the fecal transplants, which were obtained from patients with advanced melanoma who had responded to pembrolizumab, were analyzed to ensure that no infectious agents



would be transmitted. After treatment with saline and other solutions, the fecal transplants were delivered to the colons of patients through colonoscopies, and each patient also received pembrolizumab.

After these treatments, 6 out of 15 patients who had not originally responded to pembrolizumab or nivolumab responded with either tumor reduction or long-term disease stabilization. One of these patients has exhibited an ongoing partial response after more than two years and is still being followed by researchers, while four other patients are still receiving treatment and have shown no disease progression for over a year.

The treatment was well tolerated, though some of the patients experienced minor side effects that were associated with pembrolizumab, including fatigue.

The investigators analyzed the gut microbiota of all of the patients. The six patients whose cancers had stabilized or improved showed increased numbers of bacteria that have been associated with the activation of immune cells called T cells and with responses to immune checkpoint inhibitors.

In addition, by analyzing data on proteins and metabolites in the body, the researchers observed biological changes in patients who responded to the transplant. For example, levels of immune system molecules that are associated with resistance to immunotherapy declined, and levels of biomarkers that are associated with response increased.

Based on the study findings, the researchers suggest that larger clinical trials should be conducted to confirm the results and identify biological markers that could eventually be used to select patients who are most likely to benefit from treatments that alter the gut microbiome.

Research suggests that communities of bacteria and viruses in the intestines can affect the immune system and its response to chemotherapy and immunotherapy.

"We expect that future studies will identify which groups of bacteria in the gut are capable of converting patients who do not respond to immunotherapy drugs into patients who do respond," said Amiran Dzutsev, MD, PhD, of NCI's Center for Cancer Research, co-first author of the study. "These could come from patients who have responded or from healthy donors. If researchers can identify which microorganisms are critical for the response to immunotherapy, then it may be possible to deliver these organisms directly to patients who need them, without requiring a fecal transplant," he added.

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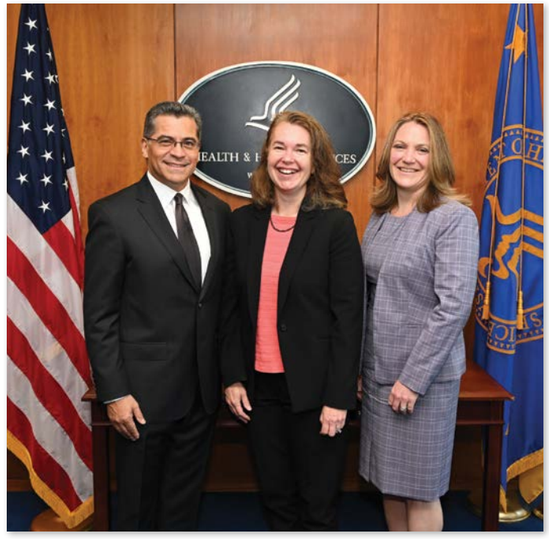
Swearing-In of Dawn O'Connell as Assistant Secretary for Preparedness and Response and Cheryl Campbell becoming Assistant Secretary for Administration

Statement by HHS Secretary Xavier Becerra

U.S. Department of Health and Human Services (HHS) Secretary Xavier Becerra swore in Dawn O'Connell as the Assistant Secretary for Preparedness and Response. O'Connell had previously served as a counselor to the Secretary, helping drive the Department's COVID-19 response.

"I have seen first-hand that Dawn O'Connell is an experienced and exceptional public servant, and I'm pleased to welcome her to the role of Assistant Secretary for Preparedness and Response. Dawn's experience as a diplomatic partner on global health issues, her strong leadership, and her role coordinating the Department-wide response to the pandemic make her well positioned to bring necessary understanding and urgency to protect Americans against the public health threats we may face. I am confident she will dutifully manage our nation's emergency preparedness and response and ensure the U.S. has capabilities and capacity to be a worldwide example of strategic and immediate pandemic and epidemic response."

Photo courtesy of HHS



Dawn O'Connell, (center), Assistant Secretary for Preparedness and Response, U.S. Department of Health and Human Services. Photo courtesy of HHS

U.S. Department of Health and Human Services (HHS) Secretary Xavier Becerra also swore in Cheryl Campbell as the Assistant Secretary for Administration (ASA). Campbell had previously served in an acting role since March.

"Cheryl Campbell brings decades of experience to the role of Assistant Secretary for Administration, and as the first woman and person of color to serve in this role, her appointment represents another step towards an administration that looks like America," said HHS Secretary Xavier Becerra. "Cheryl, a nationally recognized Health IT executive and veteran of HHS, has already laid the groundwork for 21st-century operations during her time as the Acting Assistant Secretary for Administration. I appreciate her contributions to date — particularly on our unaccompanied children response — and look forward to continue working with her to support efficient and equitable operations as HHS works to end the COVID-19 pandemic and increases health security for American Families."

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HHS Selects Emory University to Demonstrate Better Approach to Disaster Medical Care

Site becomes fourth to illustrate a regional disaster health response system

The Emory-based demonstration site becomes the fourth from ASPR designed to show the effectiveness and viability of a regional healthcare response approach to disasters. The Regional Disaster Health Response System builds on local health care coalitions and trauma centers, creating a tiered system of disaster care, similar to the model used for trauma and burn care in the United States.

The first three sites in the system, established in 2018, have demonstrated how to integrate local medical response capabilities with emergency medical services, burn centers, pediatric hospitals, labs, and outpatient services to meet the overwhelming health care needs created by disasters. The regional sites collaborate, facilitate information exchanges within the region, and develop resources to coordinate health care assets, including staff and supplies in the region.

"In past public health emergencies or natural disasters, we have witnessed thousands of people requiring immediate medical specialty care, and that surge can surpass local capacity and capability," said HHS Assistant Secretary Dawn O'Connell. "These regional demonstration sites have shown a return on investment, improving patient outcomes and reducing strain on healthcare staffs at individual facilities."

All four sites focus on integrating clinical and health care systems' operational expertise into existing preparedness and response structures at the local, state, and regional level, expanding capabilities and capacity for improving disaster readiness

Graphic courtesy of HHS Office of the Assistant Secretary for Preparedness and Response (ASPR)

Photo courtesy of Emory University

across the health care system, increasing medical surge capacity, and providing specialty care — including trauma, burn, and infectious disease, among others — during large-scale disasters or public health emergencies.

The four regional recipients will build or continue to expand systems that build a partnership for disaster health response to support clinical specialty care; align plans, policies, and procedures for clinical excellence in disasters; increase statewide and regional medical surge capacity; improve statewide and regional situational awareness; and develop metrics and test the regional system's capabilities.

ASPR is providing $1.5 million to each of the three other Regional Disaster Health Response System demonstration sites to build on accomplishments to date. These demonstration sites are based at Massachusetts General Hospital, Nebraska Medical Center, and Denver Health and Hospital Authority. Since 2018, ASPR has invested a total of $22.6 million in the Regional Disaster Health Response System.

An objective review panel of experts from professional associations, academia, and federal agencies reviewed the applications for the fourth site, and selected Emory University based on extensive criteria published in the notice of funding opportunity released in August 2021.

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Serious Complications from Youth-onset Type 2 Diabetes Arise by Young Adulthood

Findings from NIH-funded study underscore importance of early, intensive treatment

People with type 2 diabetes diagnosed during youth have a high risk of developing complications at early ages and have a greater chance of multiple complications within 15 years after diagnosis. The findings are the culmination of a first-of-its-kind trial funded largely by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), part of the National Institutes of Health.

Within 15 years of a type 2 diabetes diagnosis, 60% of participants had at least one diabetes-related complication, and nearly a third of participants had two or more complications, according to results of the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) follow-up study, called TODAY2. The findings were published in the New England Journal of Medicine.

"The original TODAY study showed that youth-onset type 2 diabetes is distinct from adult-onset diabetes — it is both more aggressive and more difficult to control," said Dr. Barbara Linder, NIDDK project scientist for TODAY. "By following this unique disease course, TODAY2 shows the devastating complications that can develop in what should be the prime of these young people's lives."

TODAY2 involved 500 original participants from the TODAY study, which began in 2004. TODAY was the first major comparative effectiveness trial for the treatment of type 2 diabetes in youth. The study compared three treatments for managing blood glucose: metformin alone, metformin plus rosiglitazone, and metformin plus an intensive lifestyle intervention. Metformin is the only oral medication approved by the U.S. Food and Drug Administration to treat type 2 diabetes in youth.

Phil Zeitler, MD, Medical Director, Children's Hospital Colorado Clinical & Translational Research Center, Section Head, Endocrinology. Photo courtesy of the Children's Hospital Colorado.

At the time of enrollment, participants were between the ages of 10-17, had been diagnosed with type 2 diabetes for fewer than two years, and were overweight or had obesity. The average age of participants after the TODAY2 follow-up was 26 years.

Participants in TODAY2 were monitored annually for signs of diabetes complications, including heart disease, kidney disease, diabetic foot complications, and to report other health events. Diabetic eye disease was assessed once during the study, at the seven-year study visit.

Overall, researchers saw a steady decline in blood glucose control over 15 years. In addition,

- 67% of participants had high blood pressure
- nearly 52% had dyslipidemia, or high fat levels in the blood
- nearly 55% had kidney disease
- 32% had evidence of nerve disease
- 51% had eye disease

Rates did not differ based on the original TODAY study treatment group assignment.

In addition, certain participants had a higher likelihood to develop multiple complications over time, with 28% developing two or more over the follow-up period. Participants who belonged to a minority racial or ethnic group, or who had high blood glucose, high blood pressure, and dyslipidemia were at higher risk for developing a complication.

"Compared to what we see in adults with type 2 diabetes, the participants in TODAY2 developed complications much earlier in their disease course and at a much faster pace over time," said TODAY2 study chair Dr. Philip Zeitler, professor of pediatrics-endocrinology at the University of Colorado School of Medicine. "This study shows the importance of treating youth-onset type 2 diabetes intensively from the beginning and using all available approaches to control blood glucose and prevent, delay, or aggressively treat developing complications."

Photo courtesy of the NIDDK

The TODAY study's diverse cohort is representative of the U.S. youth diagnosed with type 2 diabetes. Study participants had regular, intensive diabetes management through the study at no cost during the original TODAY trial, which researchers note may have actually lowered the rate of complications.

"TODAY and TODAY2 have been instrumental in understanding and treating type 2 diabetes in youth," said NIDDK Director Dr. Griffin P. Rodgers. "In addition to finding better prevention methods, discovering new and better treatment options to manage type 2 diabetes in youth will be key to ensuring their healthy futures."

The TODAY and TODAY2 studies were conducted at 15 centers in the U.S. and The George Washington University, Washington, D.C., served as the data coordinating center.

This work was completed with funding from NIDDK/NIH grant numbers U01-DK61212, U01-DK61230, U01-DK61239, U01-DK61242, and U01-DK61254; the National Center for Research Resources General Clinical Research Centers Program; and the NCRR Clinical and Translational Science Award Program.

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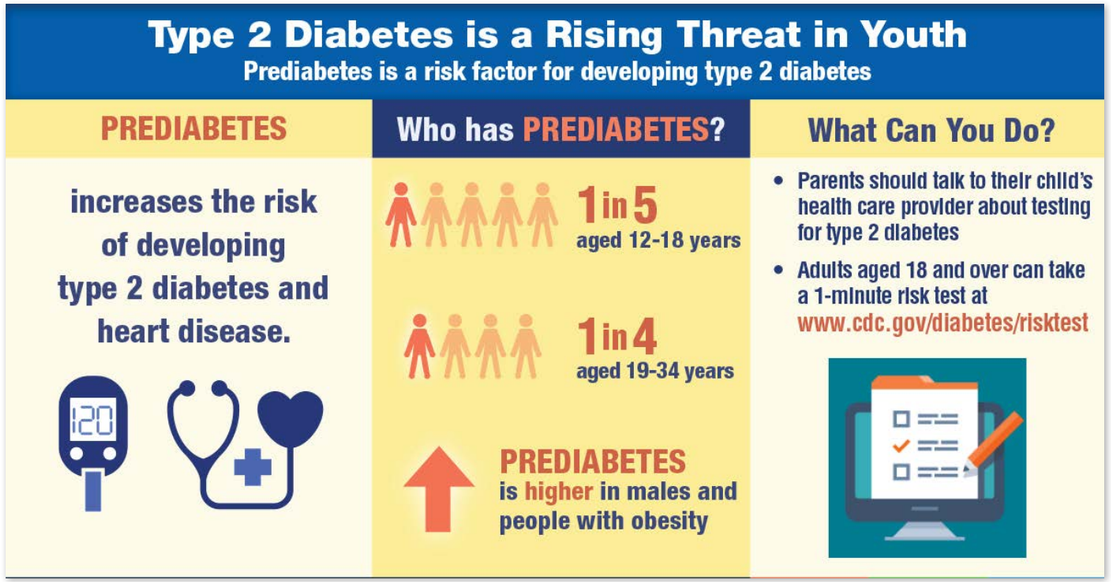
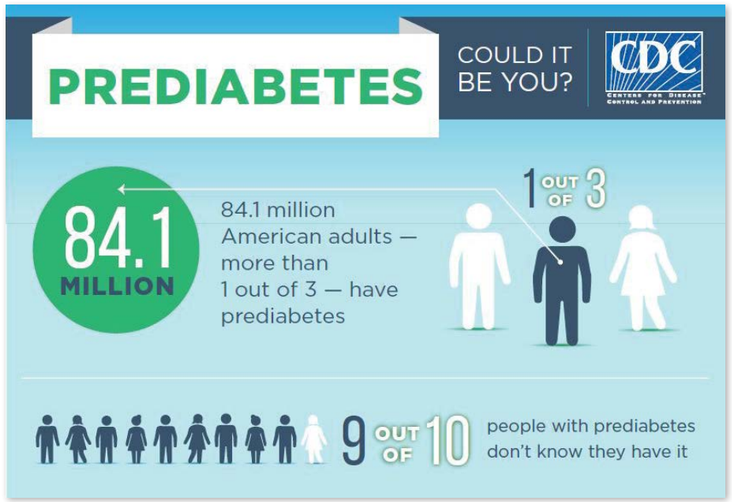


Determining What Prediabetes Means in Older Adults

Recent research suggests that we need better ways to assess the risk of future type 2 diabetes (T2D) in older adults. People with blood glucose (sugar) levels higher than normal but lower than the levels used to define diabetes are said to have "prediabetes," because they are known to be at increased risk for the disease. Fortunately for those at high-risk, the landmark NIDDK-led Diabetes Prevention Program (DPP) clinical trial demonstrated that T2D can often be prevented or delayed through diet and exercise changes designed to yield modest weight loss.

This DPP lifestyle intervention was particularly effective in older DPP participants, and the infrastructure to provide a group-based adaptation of the approach has increased nationally in recent years. Targeting those programs to people most likely to benefit from them depends on knowing who has a high likelihood of developing diabetes. There are standard definitions for prediabetes using different measurements that work fairly well for individuals who are middle aged or younger, but less is known about how well they predict the development of T2D among older individuals.

Photo courtesy of CDC



Graphic courtesy of the CDC

Researchers therefore studied a 3,412-person group of volunteers without diabetes (60 percent female; 17 percent Black; 83 percent White) who had an average age of about 75. The study tested different diagnostic criteria for prediabetes to compare how well they worked in older adults: using "HbA1c" levels; using fasting glucose levels; using either HbA1c or fasting glucose levels; or requiring the criteria for both measures to be met.

The proportion of participants diagnosed with prediabetes differed greatly depending on which criteria were applied: 29 percent if using both HbA1c and fasting glucose, 44 percent based on HbA1c levels alone, 59 percent using fasting glucose levels alone, and 73 percent according to at least one of the two measures. As expected, a higher proportion of the individuals meeting one or more criteria for prediabetes developed T2D than those who did not have prediabetes at the outset. However, for each of the individual prediabetes definitions, more of the volunteers saw their glucose or HbA1c levels improve to the normal range than progress to the diabetes range. Further, those considered to have prediabetes were also less likely to develop T2D than they were to die of any cause. Taken together, these findings suggest the need for a better test to identify future diabetes risk in people over age 70.

Article: Rooney MR, Rawlings AM, Pankow JS,...Selvin E. Risk of progression to diabetes among older adults with prediabetes NIH external link. JAMA Intern Med 181:511-519, 2021.

niddk.nih.gov

Preventive Treatment Reduces Diabetic Retinopathy Complications

In a clinical trial, early treatment with anti-vascular endothelial growth factor (VEGF) injections slowed diabetic retinopathy, a complication of diabetes that causes damage to the blood vessels of the light-sensitive tissue in the retina. However, two years into the four-year study, the early treatment's effect on vision — including changes in visual acuity and vision loss — was similar to standard treatment, which usually begins only after the onset of late disease. The intermediate findings from the DRCR Retina Network (DRCR.net) published today in JAMA Ophthalmology. The study was supported by the National Eye Institute (NEI), a part of the National Institutes of Health.

"While it is possible that preventive injections of anti-VEGF drugs may help protect vision in the longer-term, we saw no effect on vision at two years," said Raj Maturi, MD, Indiana University, Indianapolis, the protocol chair for the study. "These two-year results suggest that close monitoring and routine treatment when complications develop are key to preventing vision loss from diabetic retinopathy."

An estimated 30 million Americans have diabetes, which can cause blood vessel abnormalities, including the growth of new blood vessels in the eye. In the early stages of diabetic retinopathy, called non-proliferative diabetic retinopathy, changes in the eye's blood vessels are visible to clinicians but generally do not affect sight. In the advanced stages, people can develop proliferative diabetic retinopathy, where retinal blood vessels grow abnormally, and/or diabetic macular edema, where fluid leaks out of the retinal blood vessels. Both can lead to vision loss and blindness. Treatment, such as with anti-VEGF drugs, can slow or prevent vision loss in people with proliferative diabetic retinopathy or diabetic macular edema, if treatment occurs promptly.

In this study, participants with non-proliferative diabetic retinopathy were randomly assigned at baseline to receive either injections of Eylea (aflibercept) or a sham injection. They were examined at one, two, and four months, and then every four months for two years, receiving Eylea or sham injection at each visit. The researchers tracked their visual acuity and the severity of their diabetic retinopathy. If disease progressed, regardless of whether they were in the treatment or sham group, participants were given Eylea more frequently as is given in standard practice. If their condition did not improve with additional anti-VEGF treatment, participants could be given treatments such as laser photocoagulation or surgery if necessary.

The study included 328 participants (399 eyes). In two years, the rate of proliferative diabetic retinopathy development was 33% in the control group, compared with 14% in the treatment group. Likewise, the rate of development of diabetic macular edema affecting vision was 15% in the control group, compared with 4% in the treatment group. However, loss of visual acuity was essentially the same between the two groups at two years, suggesting that standard treatment at the appearance of proliferative diabetic retinopathy or diabetic macular edema affecting vision is sufficient to prevent further vision loss at this time point.

"We have a really good treatment for these diseases, so we can manage vision complications that may arise as disease progresses for many eyes," said Adam Glassman, Jaeb Center for Health Research, Tampa, Florida, director of the DRCR.net coordinating center. "When evaluating new preventative treatment strategies, it is important to compare them directly to the standard treatment after disease worsens, as we have done in this study."

"Although we did not see any difference in visual outcomes at two years, the four-year follow-up is going to be very important," said Jennifer Sun, MD, MPH, Joslin Diabetes Center, Harvard Medical School, Boston, chair of Diabetes Initiatives for the Network. "We look toward the four-year data to see whether reducing rates of diabetic retinopathy worsening will lead to long-term improvement in visual outcomes."

The Clinicaltrials.gov identifier for this study is NCT02634333. The study was supported by NEI and the National Institute of Diabetes and Digestive and Kidney Diseases, with funding through the Special Diabetes Program, through a cooperative agreement (EY14231). Regeneron provided aflibercept for the study and funds to DRCR Retina Network to defray the study's clinical site costs. JDRF also provided funds to defray clinical site costs.

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Century of Insulin Celebrated

By Alyssa Voss

In the summer of 1921 at the University of Toronto, after months of failed experiments, Drs. Frederick Banting and Charles Best made a profound discovery. They found that a pancreatic extract from healthy dogs reduced blood glucose in other animals with diabetes. By the following year, that extract was chemically refined and used in human clinical trials to treat people with type 1 diabetes. Called insulin, the extract would change type 1 diabetes from a fatal condition to one that could be managed.

In the 100 years since, tremendous progress has been made in diabetes research and care. By 1936, the glucose tolerance test was developed and two types of diabetes emerged: insulin-sensitive and insulin-insensitive — now known as type 1 and type 2 diabetes, respectively.

From its very beginning in 1950, NIDDK conducted and supported laboratory, clinical and population research to understand diabetes, metabolic, endocrine and related diseases.

"NIDDK has leveraged the discovery of insulin to play a critical role over the last 70 years in advancing diabetes research,"

NIH researchers study an insulin assay in the 1950s. Photo courtesy of NIH office of history.

Dr. Frederick Banting with one of his research dogs, Photo credit, Wellcome Collection.

said NIDDK director Dr. Griffin Rodgers, in a video reflecting on insulin's 100th anniversary. The reflections were part of a recent virtual symposium commemorating insulin's discovery.

During symposium opening remarks, NIH director Dr. Francis Collins said, "I look forward to witnessing the next steps that researchers presenting and attending this meeting are going to take along the path first cleared by Banting, Best and their collaborators a century ago. Let's make the next century of diabetes one where we figure out how to prevent and cure this disease so that it goes into the history books."

New Approach to Type 1 Diabetes

NIDDK-supported research made an important impact on advancing understanding about type 1 diabetes. The Diabetes Control and Complications Trial (DCCT) started in 1983 to see if people with type 1 diabetes who kept their blood glucose levels as close to normal as could safely be achieved could delay development of diabetes-related complications such as eye, kidney and nerve disease, compared with people who used the conventional treatment at the time of the study.

The trial became a landmark success. DCCT ended after 10 years in 1993 — a year earlier than planned — when the study showed that participants could significantly lower their chances of developing diabetes-related complications by keeping their blood glucose levels close to normal.

Its long-term follow-up study, called the Epidemiology of Diabetes Interventions and Complications (EDIC), has followed DCCT participants since the trial ended and showed that continuing the tight management of blood glucose levels helps people with type 1 diabetes live a normal-length life.

"The DCCT/EDIC findings were paradigm changing and were quickly adopted worldwide and incorporated into the standards of care for people living with diabetes," said Dr. William Cefalu, director of NIDDK's Division of Diabetes, Endocrinology and Metabolic Diseases (DEM). "This NIDDK-supported research favorably changed the way we view the management of diabetes forever."

Much of NIDDK's type 1 diabetes research funding comes from the Special Statutory Funding Program for Type 1 Diabetes Research, or Special Diabetes Program (SDP). This appropriation approved by Congress has provided more than $3 billion over 24 years to support innovative trials and research networks for the prevention, treatment and cure of type 1 diabetes.

SDP has supported the development of cutting-edge technologies that have made daily management of diabetes easier, such as the continuous glucose monitor (CGM). In the last few years, artificial pancreas technology has eased the management burden. The devices automatically monitor and regulate blood glucose using a CGM and insulin pump programmed with dosing algorithms tailored to the user. Through decades of NIDDK-supported clinical testing and trials, multiple artificial pancreas devices have been approved by the FDA.

Breaking Through on Type 2 Diabetes

NIDDK's role in type 2 diabetes research had an earlier start. By the 1960s, the institute began the first long-term population study among American Indians to understand causes and risk factors for type 2 diabetes and its complications. One of the first collaborations of its kind, the study was conducted in partnership with the Gila River Indian Community, the Indian Health Service and other academic partners.

NIDDK's Dr. William Knowler, chief of the NIDDK diabetes epidemiology and clinical research section in Phoenix, was a principal investigator with the study, which uncovered the alarmingly disproportionate burden of diabetes and its complications among American Indians.

"One of our important early observations was that type 2 diabetes occurs in American Indian children," Knowler said. "It was previously assumed that almost all diabetes in children was type 1 diabetes, which has a different pathogenesis from type 2 diabetes that was previously thought to occur only in adults. Type 2 diabetes is now recognized as a major form of diabetes in U.S. children, especially those from certain racial and minority groups."

NIH began studies of the Gila River Indian Community of Arizona in the 1960s. Photo courtesy of NIDDK

The study also revealed risk factors for type 2 diabetes, some of which — obesity, for instance — had the potential to be modified to reduce risk or delay onset in those at high risk.

The NIDDK-funded Diabetes Prevention Program (DPP) was launched in the 1990s to examine whether an intensive lifestyle intervention for weight loss or the medicine metformin would delay or prevent type 2 diabetes among people at high risk for the disease. Three years into the 4-year study, the trial stopped early because of the significant benefits seen among participants in both of the study's treatment groups.

The study found that people who are at high risk for type 2 diabetes can prevent or delay the disease by losing a modest amount of weight, about seven percent of their starting weight, through lifestyle changes — regular physical activity and a diet low in fat and calories. Participants in the lifestyle program reduced their incidence of diabetes by 58 percent during the 3-year study. The generic drug metformin also prevented the disease by about 31 percent.

"This was a very exciting time for all of us involved in the study," said Knowler, who also served as a DPP principal investigator. "The large magnitude of the lifestyle effect was much greater than we had hoped for. And because the intervention effects were uniform among the participants from different racial and ethnic groups, and geographic areas, the results changed the way people approach type 2 diabetes prevention worldwide."

Blazing a Future of Innovation, Better Health

As NIDDK continues to support innovative research, a new area of exploration focuses on the ways in which diabetes varies among people, even among those diagnosed with the same diabetes type. In fact, some forms of diabetes don't fit any of the known types or causes.

A new NIDDK-funded study called RADIANT (the Rare and Atypical Diabetes Network) seeks people with these unknown or uncommon forms to help understand the broad spectrum of diabetes. "Through RADIANT and other studies like it, we hope to gain insight into the more common differences present within the broad spectrum of type 2 diabetes and develop diagnostic criteria for new forms of diabetes," said Dr. Christine Lee, DEM program director and RADIANT project scientist. "Precision medicine will play a key role in the future of personalized diabetes care. Because we know that one size doesn't fit all, having precise information on prognosis and therapies for a given person will help them form diabetes care plans to meet their individual goals and preferences."

Many of the last 100 years of advances would not have been possible without the altruism of study participants. Elena Ennis, a study participant with type 1 diabetes who tested artificial pancreas technology, spoke about her experience volunteering in a trial.

"Before I had participated in my first clinical trial, I was very newly diagnosed and everything was so new to me," she said. "I was worried about what my future would look like. Participating in these trials really has given me a sense of hope as far as the future of living with diabetes. I feel like I have a large support group behind me cheering me on, because researchers are really working so hard to make things better for those of us with diabetes."

As the century since Banting and Best's discovery comes to a close, the future of diabetes research — and better prevention, management and, one day, a cure — looks bright. "NIDDK and the diabetes research community as a whole have made great progress," Rodgers said. "But our work is not done, and NIDDK will continue working toward finding prevention methods, better treatments and, one day, a cure for all types of diabetes."

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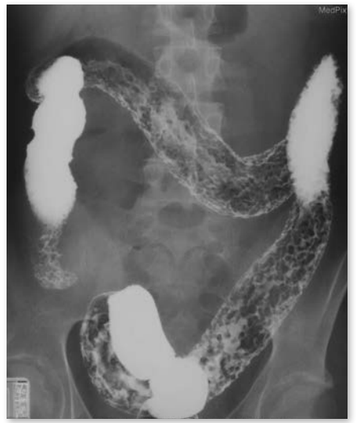
A Common Fungus Sets the Stage for Successful Fecal Microbiota Transplantation in People with Ulcerative Colitis

A recent study found that high levels of a common fungus in the gut could signal whether a microbe-based treatment would be successful for people with ulcerative colitis. Changes or disruptions in the gut's microbiome—the community of bacteria, viruses, and fungi that naturally inhabit the intestines—have been implicated in inflammatory bowel diseases like ulcerative colitis. One treatment that researchers are investigating is fecal microbiota transplantation (FMT), whereby a sample containing gut microbes from a healthy donor is introduced into a person with colitis to help reestablish a more functional gut microbiome. While FMT has proven to be a successful therapy for people with Clostridioides difficile (C. diff) bacterial infections, with over 90 percent of people cured after a single treatment, FMT is less successful for people with ulcerative colitis: in a recent clinical trial, less than half the participants with colitis experienced remission after FMT.



Double contrast barium enema with prone and supine views indicating shortening of the colon and loss of haustral folds mimicking a lead pipe. Areas of ulceration of the mucosa are seen from rectum to cecum, they are continuous and become less prominent proximally. Contrast is seen passing through the ileocecal valve. The appendix was not seen. Photo courtesy of the National Library of Medicine.

Knowing why the treatment works only in some people is important, because it would allow health care providers to predict which individuals with ulcerative colitis would benefit from FMT as opposed to another treatment strategy. One possibility is that FMT's success may be dependent upon the makeup of the recipient's microbiome. For example, FMT is less likely to succeed as a C. diff treatment for people who have high levels of Candida, a type of fungus found in the guts of nearly everyone. Candida is an opportunistic pathogen that can exacerbate inflammation when the immune system is weakened or the microbiome is disrupted. Moreover, high levels of Candida could determine FMT outcomes by affecting the levels of other microbial members of the gut. Thus, like in people with C. diff, high levels of Candida may also play an important role in determining the outcomes of FMT in people with ulcerative colitis.

To determine whether gut microbes such as Candida may be affecting FMT for people with ulcerative colitis, researchers studied the microbiomes of 24 men and women who had received FMT as a trial treatment for the disease. Unlike in people with C. diff infections, the study participants who had higher levels of Candida before FMT were more likely to have improved colitis symptoms and clinical features following treatment. After FMT, levels of Candida — and the immune response against Candida — were lower in these people compared to those who received a placebo. This raises the possibility that introducing gut microbes from healthy donors suppresses the overgrowth of Candida — and the inflammation caused by it — in people with ulcerative colitis.

The researchers also found that study participants who had higher pre-FMT levels of Candida were more likely to have higher pre-FMT levels of certain gut bacteria that have been linked to successful FMT outcomes for ulcerative colitis. This suggests that a high level of Candida may create a permissive environment for FMT in people with ulcerative colitis by encouraging the growth of specific gut bacteria in the microbiome. Overall, the results of this study hint of an intricate relationship between Candida and other members of the microbiome, whereby high levels of Candida in people with ulcerative colitis make the microbiome more receptive to FMT. In turn, FMT results in reduced levels of Candida and the inflammation associated with it. In this manner, Candida levels could be a promising marker to predict whether FMT may be effective for people with ulcerative colitis.

Article: Leonardi I, Paramsothy S, Doron I,…Iliev ID. Fungal trans-kingdom dynamics linked to responsiveness to fecal microbiota transplantation (FMT) therapy in ulcerative colitis NIH. Cell Host Microbe 27: 823-829. e3, 2020.

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NIH Scientists Find that Salmonella Use Intestinal Epithelial Cells to Colonize the Gut

The immune system's attempt to eliminate Salmonella bacteria from the gastrointestinal (GI) tract instead facilitates colonization of the intestinal tract and fecal shedding, according to National Institutes of Health scientists. The study, published in Cell Host & Microbe, was conducted by National Institute of Allergy and Infectious Diseases (NIAID) scientists at Rocky Mountain Laboratories in Hamilton, Montana.

Salmonella Typhimurium bacteria (hereafter Salmonella) live in the gut and often cause gastroenteritis in people. The Centers for Disease Control and Prevention estimates Salmonella bacteria cause about 1.35 million infections, 26,500 hospitalizations and 420 deaths in the United States every year. Contaminated food is the source for most of these illnesses. Most people who get ill from Salmonella have diarrhea, fever and stomach cramps but recover without specific treatment. Antibiotics typically are used only to treat people who have severe illness or who are at risk for it.

Salmonella bacteria also can infect a wide variety of animals, including cattle, pigs and chickens. Although clinical disease usually resolves within a few days, the bacteria can persist in the GI tract for much longer. Fecal shedding of the bacteria facilitates transmission to new hosts, especially by so-called "super shedders" that release high numbers of bacteria in their feces.

NIAID scientists are studying how Salmonella bacteria establish and maintain a foothold in the GI tract of mammals. One of the first lines of defense in the GI tract is the physical barrier provided by a single layer of intestinal epithelial cells.

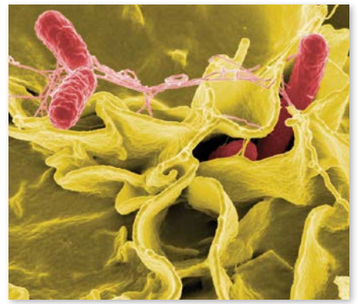
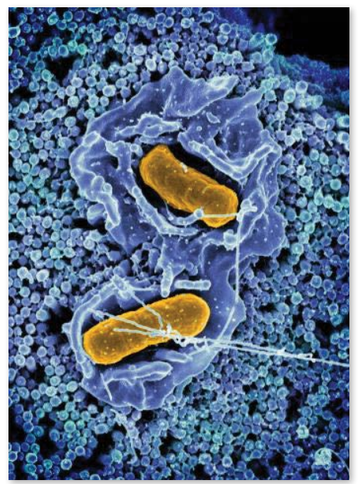


Photo courtesy of NIH

These specialized cells absorb nutrients and are a critical barrier that prevents pathogens from spreading to deeper tissues. When bacteria invade these cells, the cells are ejected into the gut lumen — the hollow portion of the intestines.



Scanning electron micrograph of Salmonella Typhimurium invading a human epithelial cell. Photo courtesy of NIAID

However, in previous studies, NIAID scientists had observed that some Salmonella replicate rapidly in the cytosol — the fluid portion — of intestinal epithelial cells. That prompted them to ask: does ejecting the infected cell amplify rather than eliminate the bacteria?

To address this question, the scientists genetically engineered Salmonella bacteria that self-destruct when exposed to the cytosol of epithelial cells but grow normally in other environments, including the lumen of the intestine. Then they infected laboratory mice with the self-destructing Salmonella bacteria and found that replication in the cytosol of mouse intestinal epithelial cells is important for colonization of the GI tract and fuels fecal shedding. The scientists hypothesize that, by hijacking the epithelial cell response, Salmonella amplify their ability to invade neighboring cells and seed the intestine for fecal shedding.

The researchers say this is an example of how the pressure exerted by the host immune response can drive the evolution of a pathogen, and vice versa. The new insights offer new avenues for developing novel interventions to reduce the burden of this important pathogen.

Article

A Chong et al. Cytosolic replication in epithelial cells fuels intestinal expansion and chronic fecal shedding of Salmonella Typhimurium. Cell Host & Microbe DOI: 10.1016/j.chom.2021.04.017 (2021).

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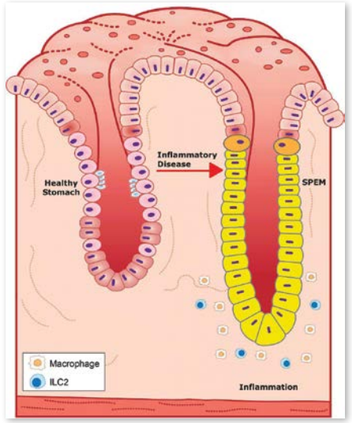
Male Hormones Regulate Stomach Inflammation in Mice

Scientists at the National Institutes of Health determined that stomach inflammation is regulated differently in male and female mice after finding that androgens, or male sex hormones, play a critical role in preventing inflammation in the stomach. The finding suggests that physicians could consider treating male patients with stomach inflammation differently than female patients with the same condition. The study was published in Gastroenterology.

Researchers at NIH's National Institute of Environmental Health Sciences (NIEHS) made the discovery after removing adrenal glands from mice of both sexes. Adrenal glands produce glucocorticoids, hormones that have several functions, one of them being suppressing inflammation. With no glucocorticoids, the female mice soon developed stomach inflammation. The males did not. However, after removing androgens from the males, they exhibited the same stomach inflammation seen in the females.

"The fact that androgens are regulating inflammation is a novel idea," said co-corresponding author John Cidlowski, PhD, deputy chief of the NIEHS Laboratory of Signal Transduction and head of the Molecular Endocrinology Group. "Along with glucocorticoids, androgens offer a new way to control immune function in humans."

While this study provides insight into how inflammation is being regulated in males, Cidlowski said additional research is underway to understand the process in females. The scientist handling this phase of research is co-corresponding author Jonathan Busada, PhD,



Glucocorticoids and androgens promote a healthy stomach pit by inhibiting inflammation, left, while their absence promotes inflammation and SPEM seen in a diseased pit, right. SPEM glands are also much larger than healthy stomach glands. Graphic courtesy of Jonathan Busada, PhD/NIEHS

assistant professor at West Virginia University School of Medicine in Morgantown. When Busada started the project several years ago, he was a postdoctoral fellow working in Cidlowski's group.

Whether inflammation is inside the stomach or elsewhere in the body, Busada said rates of chronic inflammatory and autoimmune diseases vary depending on sex. He said eight out of 10 individuals with autoimmune disease are women, and his long-term goal is to figure out how glucocorticoids and androgens affect stomach cancer, which is induced by chronic inflammation.

The current research focused on stomach glands called pits, which are embedded in the lining of the stomach.

Busada said the study showed that glucocorticoids and androgens act like brake pedals on the immune system and are essential for regulating stomach inflammation. In his analogy, glucocorticoids are the primary brakes and androgens are the emergency brakes.

"Females only have one layer of protection, so if you remove glucocorticoids, they develop stomach inflammation and a pre-cancerous condition in the stomach called spasmolytic polypeptide-expressing metaplasia (SPEM)," Busada said. "Males have redundancy built in, so if something cuts the glucocorticoid brake line, it is okay, because the androgens can pick up the slack."

The research also offered a possible mechanism — or biological process — behind this phenomenon. In healthy stomach glands, the presence of glucocorticoids and androgens inhibit special immune cells called type 2 innate lymphoid cells (ILC2s). But in diseased stomach glands, the hormones are missing. As a result, ILC2s may act like a fire alarm, directing other immune cells called macrophages to promote inflammation and damage gastric glands leading to SPEM and ultimately cancer.

"ILC2s are the only immune cells that contain androgen receptors and could be a potential therapeutic target," Cidlowski said.

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Secretary Becerra Delivers Remarks at White House World AIDS Day Event

By Xavier Becerra, Secretary of the Department of Health and Human Services

President Biden and HHS Secretary Becerra deliver remarks to commemorate World AIDS Day, launch the National HIV/AIDS Strategy, and kick off the Global Fund Replenishment process. As Prepared for Delivery:

Good afternoon, everyone. Let me start by thanking President Biden and the White House for hosting us, and for their steadfast leadership over the past year.

I also want to thank our extraordinary team at HHS: Dr. Francis Collins, Dr. Rochelle Walensky, Dr. Anthony Fauci, Admiral Rachel Levine, Surgeon General Vivek Murthy, Assistant Secretary Loyce Pace, and so many other leaders who help our Department improve the health and well-being of the American people.

And finally, I want to recognize the generations of activists who have made their voices heard in the fight against HIV. People like Pedro Zamora, an HIV educator and television star who died of AIDS-related complications in 1994.

Before his passing, Pedro asked the world a simple question. He said, "I wonder now, as I look around me, who is going to pick up my torch?". Today, we are still fighting to end the HIV epidemic. But we have not let Pedro's torch be extinguished. Nor have we forgotten the 36 million people who have died from AIDS-related illnesses around the globe.

As Secretary of Health and Human Services, I'm proud to lead a department and serve in an administration that is confronting the HIV epidemic head on. Look no further than the new National HIV/AIDS Strategy that President Biden released today.

Over the past few months, HHS has worked together with the White House and other agencies to develop a whole-of-society response to the HIV epidemic. This strategy provides a roadmap for ending the epidemic by advancing equity, expanding resources, and engaging those who have lived this struggle, including:

- Gay, bisexual, and other men who have sex with men;
- Racial and ethnic minorities, especially African Americans and Latinos;
- Transgender women and heterosexual women;

Xavier Becerra, Secretary, Department of Health and Human Services

- People who use drugs; and
- People experiencing homelessness or unstable housing.

HHS will play a critical role in implementing this strategy. And we're already leading the way through the Ending the HIV Epidemic in the U.S. initiative (EHE). Like the new HIV Strategy, the EHE initiative is focused on ending this epidemic by 2030.

EHE will provide additional support to the 50 jurisdictions where more than half of the country's new HIV diagnoses occur, as well as seven states with a disproportionate occurrence of HIV in rural areas. And I will be working closely with my Assistant Secretary for Health, Admiral Rachel Levine, and the Presidential Advisory Council on HIV/AIDS to support this new national strategy.

Our HHS agencies will also continue to support the global fight to end HIV through the President's Emergency Plan for AIDS Relief (PEPFAR). We're working with countries around the world to train health care workers and improve detection, apply the latest research and safest medications, and provide life-saving treatment to those in need. We're partnering with the World Health Organization and others to advance critical policies that will save lives. And last month, the United States announced that we will be hosting the Global Fund's Seventh Replenishment Conference.

Back in June, HHS marked the 40th anniversary of the first official report about AIDS in 1981. We have come a long way in the last four decades. But as this year's World AIDS Day theme reminds us, we still have plenty of work to do to ensure equitable access to HIV services and end this epidemic.

And we need everyone's voice to make that happen — we all have a role to play, whether we are in government, health care, the private sector, or community-based organizations.

On World AIDS Day, we remember all those we've lost. The faces in the frames. The names on the quilt. The millions gone too soon. Let's honor them the best way we know how: By picking up their torch and keeping it burning. Thank you.

hhs.gov

About Xavier Becerra

Xavier Becerra is the 25th Secretary of the Department of Health and Human Services and the first Latino to hold the office in the history of the United States. As Secretary, he will carry out President Biden's vision to build a healthy America, and his work will focus on ensuring that all Americans have health security and access to healthcare.

Throughout his career, the Secretary has made it his priority to ensure that Americans have access to the affordable healthcare they need to survive and thrive — from his early days as a legal advocate representing individuals with mental illness, to his role as the Attorney General of the state of California.

Secretary Becerra served 12 terms in Congress as a member of the U.S. House of Representatives. During his tenure, he was the first Latino to serve as a member of the powerful Committee on Ways and Means, he served as Chairman of his party's caucus, and as the Ranking Member of the Ways and Means Subcommittee on Social Security and Ranking Member of the Subcommittee on Health.

For over two decades in Congress, Secretary Becerra worked so that every family had the assurance of care that his own family had when he was growing up. As a member of the Ways and Means Committee, Secretary Becerra introduced legislation — the Medicare Savings Programs Improvement Act of 2007 — that expanded cost-sharing subsidies for low-income seniors who receive both Medicare and Medicaid benefits by increasing the amount of resources they could receive. He championed provisions of the Medicare Improvements for Patients and Providers Act of 2008 that required physicians who perform imaging to be accredited and trained to ensure patient safety. And he was one of the original cosponsors of the Patient Protection and Affordable Care Act (ACA) which strengthened Medicare and lowered costs for seniors.

As Attorney General of the state of California, Secretary Becerra helped to promote competition by taking on a number of pharmaceutical companies that restricted competition through "pay-for-delay" schemes, held several companies accountable for legal violations for not protecting patients' health information, and took action early in the pandemic to keep Californians safe by using his authority to protect workers from exposure to COVID-19, secure key safeguards for frontline health care workers' rights, and take on fraudsters trying to take advantage of people during the pandemic. In addition, he cracked down on Medicare and Medicaid fraud, acted to combat the opioid crisis, including holding drug makers accountable, won an unprecedented $575 million antitrust settlement against one of the largest health systems in California, and he led the three-year federal court fight to save the ACA and with it, the protections of the 133 million Americans with preexisting conditions.

Born in Sacramento Secretary Becerra is the son of working-class parents. He was the first in his family to receive a four-year degree, earning his Bachelor of Arts in Economics from Stanford University. He earned his Juris Doctorate from Stanford Law School. His mother was born in Jalisco, Mexico and immigrated to the United States after marrying his father, a day laborer turned construction worker. He is married to Dr. Carolina Reyes, and he is proud of his three daughters: Clarisa, Olivia and Natalia, and son-in-law Ivan.

HRSA Promotes Access to Gender Affirming Care and Treatment in the Ryan White HIV/AIDS Program

By Laura Cheever, MD, ScM, Associate Administrator for the HIV/AIDS Bureau, Health Resources and Services Administration, U.S. Department of Health and Human Services

In December 2021 the Health Resources and Services Administration (HRSA) released a letter encouraging Ryan White HIV/AIDS Program (RWHAP) service providers to leverage their existing infrastructure to provide access to gender affirming care and treatment services for transgender and gender diverse people with HIV. This guidance supports HRSA's efforts to address health disparities and reduce barriers to lifesaving HIV care, medication, and support services for people of transgender experience with HIV so they can lead long, healthy lives.

Photo courtesy of the City of Minneapolis

The letter issued by HRSA's HIV/AIDS Bureau reaffirms the importance of providing culturally affirming health care and social services to the transgender community as a key component of improving their lives. This includes housing, behavioral and mental health services, and medical care and medication, all of which are fundamental to reducing health disparities and improving HIV-related outcomes among transgender people.

RWHAP Initiatives to Support Transgender People with HIV

The RWHAP program serves more than 50 percent of all people with diagnosed HIV in the United States. Of the more than 561,000 people served by the RWHAP in 2020, 2.1 percent, approximately 11,600 were transgender. A number of HRSA funded initiatives support patient-centered, trauma-informed, and inclusive environments of care for transgender RWHAP clients to help reduce medical mistrust and other barriers to antiretroviral therapy adherence. Some examples of our work include:

- Using Evidence-Informed Interventions to Improve Health Outcomes for People Living with HIV (E2i) Initiative: A project funded by the RWHAP Part F Special Projects of National Significance (SPNS) to identify and provide support for the implementation of evidence-informed interventions to reduce HIV-related disparities and improve health outcomes. One of E2i's focus areas is improving HIV outcomes for transgender women.
- HIV Care Continuum Interventions for Transgender Women: A Topical Review: A recently published manuscript from the E2i project that outlines findings from a literature review on interventions designed to improve at least one HIV care continuum outcome or address one barrier to achieving HIV care continuum outcomes among transgender women with diagnosed HIV in the United States.
- A previously funded RWHAP Part F SPNS initiative, the Transgender Women of Color Initiative, focused specifically on transgender women of color with HIV. Each of the initiative's nine demonstration sites developed innovative models for linking and retaining transgender women of color in HIV care. The intervention manuals from these demonstration sites are available on the TargetHIV website .
- The RWHAP Services Report (RSR): This report fills an important gap in national HIV data about transgender people with HIV. The RSR uses a two-step method for determining gender identity, which first identifies sex assigned at birth, followed by current gender identity (male, female, transgender female, transgender male, and other gender identity). To explore RWHAP client characteristics and outcomes, please see our RWHAP Compass Dashboard and the 2020 RWHAP Annual Client-Level Data Report.

Among transgender clients receiving RWHAP HIV medical care in 2020, 84.5 percent were virally suppressed, which is higher than the national average among all people with diagnosed HIV in the U.S., but it is lower than the national RWHAP average (89.4 percent). We recognize that we need to do more to support this community.

To help achieve the goals of the National HIV/AIDS Strategy, including achieving health equity and ending the HIV epidemic, we will continue to support and share evidence-based, evidence-informed, and emerging interventions that focus on improving the health and lives of transgender and gender diverse people with HIV.

hiv.gov

NIH Statement on World AIDS Day

Statement of Anthony S. Fauci, MD, Director, National Institute of Allergy and Infectious Diseases, and Maureen M. Goodenow, PhD, Associate Director for HIV/AIDS Research and Director, NIH Office of AIDS Research, National Institutes of Health

Since 1988, World AIDS Day has been an annual call to end the HIV/AIDS pandemic as we remember the many who lost their lives to the disease. Considerable progress has been made since the first World AIDS Day; however, far too many people continue to acquire HIV and die from its related illnesses. In 2020, an estimated 680,000 people globally died from HIV-related causes, and roughly 1.5 million people became newly infected with HIV, according to the World Health Organization (WHO).

Graphic courtesy of floridahealth.gov

Remarkable scientific progress achieved over the past four decades has led to highly effective HIV treatment and prevention strategies. Unfortunately, these life-saving tools are not reaching all the people who most need them. The theme for World AIDS Day 2021 is Ending the HIV Epidemic: Equitable Access, Everyone's Voice. Equity must be a goal for every researcher, public health official, healthcare worker, and advocate working to address HIV/AIDS.

Here in the United States, HIV remains a major healthcare challenge that disproportionately affects marginalized groups, such as members of the Black/African-American and Latinx communities, women, people who use drugs, men who have sex with men, and transgender women. A part of U.S. government efforts to end the epidemic in the United States, NIH research plays a key role in the HIV National Strategic Plan: A Roadmap to End the Epidemic, and its goal of reducing new HIV cases by at least 90% in 2030.

Antiretroviral therapy (ART) is the cornerstone of both HIV treatment and prevention. It is highly effective at both preserving the health of the person with HIV (PWH) and eliminating the risk of transmitting the virus to others. Global promotion of

Anthony S. Fauci, MD

the "undetectable equals untransmissible", or U=U, approach has helped raise awareness that people on ART with undetectable levels of virus do not transmit HIV to their sexual partners. However, too few PWH are consistently receiving and adhering to ART regimens. As of the end of 2020, an estimated 27.5 million PWH worldwide were taking ART — two-thirds of the universal treatment target set by UNAIDS.

Long-acting ART (cabotegravir) delivered via monthly injection, which was approved in the United States earlier this year, may prove preferable for some people to currently available daily, oral medications. Ongoing research suggests that future formulations could potentially extend the injection time to every 6 months to a year, perhaps making the approach even more appealing as a treatment option. Long-acting antiretroviral medication via injection will also soon be considered for regulatory approval as pre-exposure prophylaxis.

Maureen M. Goodenow, PhD

In other encouraging developments in HIV prevention, broadly neutralizing antibodies (bNAbs) are also considered promising candidates for long-acting HIV prevention. In research findings announced earlier this year, an investigational bNAb delivered intravenously once every eight weeks safely and effectively prevented acquisition of certain HIV strains when tested in two multinational clinical trials. The antibodies are expected to play a key role in future development of long-acting HIV prevention tools and vaccines.

Although the HIV vaccine field has been marked by disappointing results over the years, finding a safe, effective and durable HIV vaccine remains an NIH priority. Currently, the Phase 3 Mosaico/HPTN 706 HIV vaccine clinical trial is underway in the Americas and Europe with results expected in 2024. Lessons learned from highly effective SARS-CoV-2 vaccines also offer an encouraging path forward for HIV vaccine discovery by providing applications for new vaccine platforms, such as mRNA, and novel strategies for rapidly identifying vaccine targets. Additionally, promising outcomes utilizing bNAbs suggest it may be possible to achieve an HIV vaccine with a high level of efficacy — an almost inconceivable scientific possibility several years ago.

To address the intertwined substance use and overdose crises and the HIV epidemic, our HIV strategy must work to understand the intersectional influence of social and structural factors, embrace evidence-based harm-reduction strategies, such as syringe services programs, and include efforts to overcome stigma and other barriers to care among people who use drugs. This year, NIH announced a new trial, INTEGRA, or HPTN 094, to study how best to integrate substance use, mental health, and HIV services to forge new paths to recovery from addiction and mental illness and offer lifesaving opportunities to diagnose, prevent and treat HIV.

As the concurrent battles against the HIV/AIDS and COVID-19 pandemics continue, we applaud the commitment and passion of HIV clinical trial participants, scientists, health care professionals, policymakers, and advocates. We continue to stand with you in the critical work needed to optimize strategies for improving the health of those with HIV, prevent new cases, and achieve a durable end to HIV/AIDS.

niaid.nih.gov

Photo courtesy of usaid.gov

To End HIV Epidemic, We Must Address Health Disparities

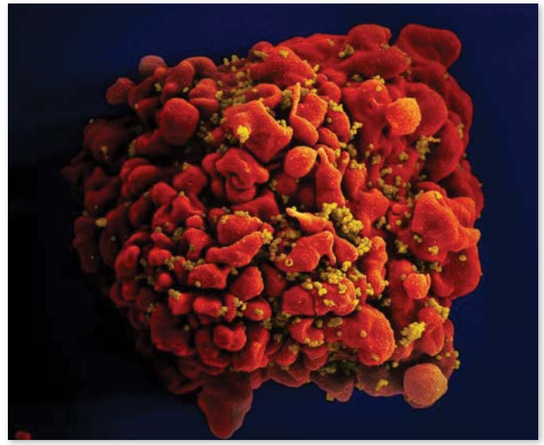
Expert report cites unequal progress in Southern U.S. and among marginalized groups.

Scientific strides in HIV treatment and prevention have reduced transmissions and HIV-related deaths significantly in the United States in the past two decades. However, despite coordinated national efforts to implement HIV services, the epidemic persists, especially in the South. It also disproportionately impacts marginalized groups, such as Black/African-American and Latinx communities, women, people who use drugs, men who have sex with men, and other sexual and gender minorities. Following the release of the HIV National Strategic Plan and marking two years since the launch of the Ending the HIV Epidemic: A Plan for America (EHE) — a U.S. Department of Health and Human Services initiative to reduce new HIV transmissions by at least 90% by 2030 — researchers, advocates, and other stakeholders reported on the HIV epidemic response in The Lancet HIV in the USA Series.

Literature reviews, commentaries, and data analyses in the series outline recommendations to overcome barriers to implementing HIV services, such as counseling, testing, treatment, pre-exposure prophylaxis (PrEP), and syringe services programs. These services are critical to preventing new HIV transmissions and helping people living with HIV achieve and maintain a "durably undetectable" viral load (the amount of HIV in the blood). Maintaining an undetectable viral load both preserves individual health and eliminates the risk of sexually transmitting the virus to others, a concept known as Undetectable = Untransmittable (U=U). By leveraging these services and addressing structural barriers, the experts argued, the EHE goals remain attainable and important, even as the COVID-19 pandemic presents new challenges and exacerbates existing health disparities.

The series was funded in part by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health within HHS. The authors received additional support from the NIH-funded Centers for AIDS Research and NIH's National Institute of Allergy and Infectious Diseases (NIAID).

"Scientific advances have transformed the course of HIV in individuals. To transform the course of the epidemic, we need to expand care and prevention strategically to those who need it most," said NIDA Director Nora D. Volkow, MD. "That means taking a hard look at who has been excluded from services and take immediate steps to overcome systemic barriers like stigma, structural racism, and other forms of discrimination to connect



Scanning electron micrograph of an HIV-infected H9 T cell. Photo courtesy of NIAID

hardly reached people — such as individuals with substance use disorders — with HIV testing, prevention, and treatment."

The series' authors recommend allocating resources to the areas and populations most hard-hit by the HIV epidemic, especially the U.S. South, where 52% of new HIV transmissions occurred in 2018 despite being home to only 37% of the U.S. population. The recommendation echoes a key EHE strategy to prioritize the 57 counties, U.S. territories, and states in which more than half of U.S. HIV transmissions occurred in 2016 and 2017 for targeted interventions.

"To end the HIV epidemic, we must continue to develop and deploy novel HIV treatment and prevention strategies suited to the different needs and preferences of diverse populations disproportionately affected by HIV," says NIAID Director Anthony S. Fauci, M.D. "It is also essential that HIV health services continue during the COVID-19 pandemic."

The authors explained that stark disparities in HIV outcomes also exist between certain age, racial, and ethnic groups, as well as between sexual and gender identities. While HIV diagnoses decreased overall and among white men who have sex

Photo courtesy of NIH

with men between 2009 and 2018, new cases remained stable among Black/African-American men who have sex with men and increased among young people aged 25-34 and Latino men who have sex with men. While Blacks/African Americans make up only about 13% of the U.S. population, they accounted for 43% of HIV-related deaths in 2018. Researchers suggested that culturally appropriate, tailored interventions may help communities respond to the unique needs of people in — or at the intersections of — these groups.

Such interventions to promote HIV prevention and treatment adherence, the authors suggested, should take a multi-faceted approach and address the whole individual.

"We have incredible tools to prevent and treat HIV, but people may not fully utilize them if they are facing personal or structural issues that pose more immediate hardship like substance use and mental health disorders," said Chris Beyrer, MD, MPH, investigator at the Johns Hopkins Bloomberg School of Public Health, Baltimore, and a lead author on the series. "You may struggle to take a daily medication if you are facing food insecurity or cannot find affordable treatment for your substance use disorder."

The authors detailed additional economic barriers to accessing HIV health services in the United States. These included unequal access to Medicaid, on which 40% of people living with HIV rely, depending on one's state of residence. The series' authors recommended implementing universal healthcare coverage and expanding safety net programs for the uninsured or underinsured, such as the Ryan White HIV/AIDS Program , on which 82% of uninsured people living with HIV rely for medical care.

Stigma, discrimination, and bias by healthcare providers were among major barriers to care identified by the series authors and disproportionately affected marginalized racial groups, people who use drugs, and sexual and gender minorities. Healthcare professionals may help address these concerns by cultivating informed, supportive care practices that integrate mental health care and substance counselling. Because internalized HIV stigma can also negatively affect a person's mental health and adherence to medication, the authors recommended promoting awareness of U=U through a national campaign.

While the series' authors cite a large body of HIV research in making these recommendations, they also highlighted opportunities for additional research that could help end the HIV epidemic. Women make up one out of every four people living with HIV in the United States, and rates of HIV transmission are high among transgender people, demonstrating the need for continued efforts to ensure the needs of these populations are taken into account at all stages of clinical research. The authors also supported continued investment in efforts to develop a preventive HIV vaccine and HIV cure, both of which would accelerate an end to the HIV epidemic in the U.S. and around the globe.

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Too Many People with HIV Fail to Achieve Durable Viral Suppression

NIH-funded study estimates global progress toward UNAIDS goal

Among people with HIV worldwide who are receiving antiretroviral therapy (ART), adults are getting closer to the global target of 95% achieving viral suppression, but progress among children and adolescents is lagging and long-term viral suppression among all groups remains a challenge. These findings of a study funded by the National Institutes of Health suggest that substantial efforts are needed to help people with HIV durably suppress the virus. The findings were published today in the journal The Lancet HIV.

HIV Awareness Ribbon. Photo courtesy of NIAID

People with HIV who achieve viral suppression protect their immune health and prevent transmitting HIV to others. In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) set a goal of 95% of all people with HIV who are taking ART achieving viral suppression by 2030.

Scientists from the National Institutes of Health-funded International epidemiology Databases to Evaluate AIDS (IeDEA) consortium set out in 2020 to estimate how close the world is to achieving that goal. The study was led by Win Min Han, MBBS, MSc, a PhD student-researcher at the Kirby Institute of the University of New South Wales in Sydney, Australia; Azar Kariminia, PhD, a senior lecturer at the Kirby Institute; and Matthew G. Law, PhD, head of the Biostatistics and Databases Program and professor of biostatistics at the Kirby Institute. Funding for IeDEA comes from the National Institute of Allergy and Infectious Diseases (NIAID), part of NIH, and from eight other NIH institutes and centers.

The investigators analyzed data from 148 IeDEA treatment sites in 31 countries on five continents to estimate the proportions of children, adolescents and adults who were virally suppressed one, two and three years after initiating ART. The data came from more than 21,500 children and adolescents with HIV aged 17 years or younger and more than 255,000 adults with HIV, all of whom had begun receiving ART between 2010 and 2019. Viral suppression was defined as having fewer than 1,000 copies of HIV per milliliter of blood.

The researchers calculated the percentages of children and adults who were virally suppressed based on data from those who were alive, in follow-up, and had viral load measurements for up to three years of ART. To further estimate viral suppression among people who had fallen out of HIV care during a three-year interval, the investigators looked to a Zambian study of viral suppression rates in a similar population and calculated an adjustment to viral suppression rates in the IeDEA population.

The researchers estimated that among adults, 79% were virally suppressed after one year of ART, 72% after two years and 65% after three years. Among children and adolescents, 64% were virally suppressed after one year of ART, 62% after two years and 59% after three years. These viral suppression rates illustrate how much farther global HIV treatment programs need to go to reach and sustain the UNAIDS 2030 targets, according to the investigators. Importantly, the even lower rates of viral suppression among children and adolescents with HIV underscore the need to improve approaches for achieving durable viral suppression in these age groups.

Article

WM Han et al. Global estimates of viral suppression in children and adolescents and adults on antiretroviral therapy adjusted for missing viral load measurements: a multiregional, retrospective cohort study in 31 countries(link is external). The Lancet HIV (2021).

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Disease Surveillance Among U.S.-Bound Immigrants and Refugees

Electronic Disease Notification System, United States, 2014–2019

Christina R. Phares, PhD[1]; Yecai Liu, MS[1]; Zanju Wang, MS[1]; Drew L. Posey, MD[1]; Deborah Lee, MPH[1]; Emily S. Jentes, PhD[1]; Michelle Weinberg, MD[1]; Tarissa Mitchell, MD[1]; William Stauffer, MD[1,2]; Julie L. Self, PhD[3]; Nina Marano, DVM[1]

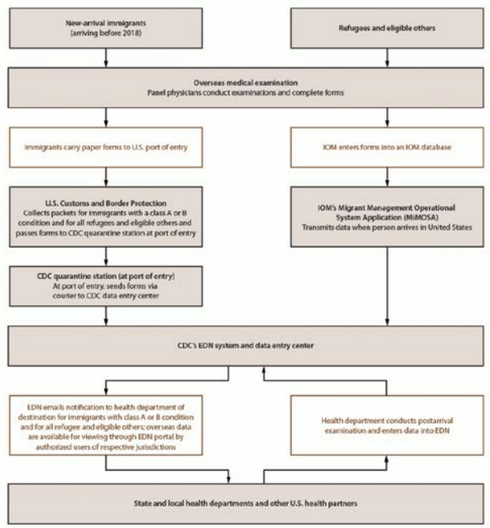
Each year, approximately 500,000 immigrants and tens of thousands of refugees and eligible others move to the United States after applying for admission while overseas (any country other than the United States and its territories). Eligible others are persons who although not classified as refugees (e.g., certain parolees, special immigrant visa holders, and follow-to-join asylees) are eligible for the same services and benefits as refugees. As part of the admission process, these immigrants, refugees, and eligible others undergo an overseas medical examination to determine medical admissibility. The U.S. Department of Health and Human Services (HHS) has the regulatory authority to require this examination[1–4] and describes these requirements in technical instructions issued by CDC. As of 2019, the examinations were conducted by approximately 600 licensed panel physicians appointed by the U.S. Department of State (DOS), working in 350 clinics in 160 countries.

The overseas medical examination identifies applicants with class A and class B conditions. An applicant with a class A communicable disease cannot be admitted to the United States until the disease has been successfully treated or the U.S. Department of Homeland Security (DHS) grants a waiver. When a class A condition resolves, the applicant is reclassified as having a class B condition and is allowed to travel to the United States. The U.S. Code of Federal Regulations specifies four class A communicable diseases of public health significance: tuberculosis (TB) disease, infectious syphilis, gonorrhea, and infectious Hansen's disease. Persons with class B conditions can be admitted; however, the condition might require treatment or follow-up. Persons with class B TB include those who have successfully completed treatment overseas for TB disease (class B0), those with signs or symptoms suggestive of TB disease but whose overseas laboratory tests and clinical examinations ruled out current infectious TB disease (class B1), those with a diagnosis of latent TB infection (LTBI) (class B2), and the close contacts of persons known to have TB disease (class B3).

In addition to the four specified conditions, other class A communicable diseases include quarantinable communicable diseases; these diseases are designated by a presidential executive order and are, currently, infectious TB, cholera, diphtheria, measles, plague, smallpox, yellow fever, viral hemorrhagic fevers, severe acute respiratory syndromes (COVID-19, Middle East respiratory syndrome, and severe acute respiratory syndrome [SARS], and influenza caused by novel or reemergent influenza)[5], and communicable diseases posing a public health emergency of international concern (PHEIC)[6] that could be imported into the United States and affect U.S. residents. With the exception of infectious TB, data about quarantinable and PHEIC conditions are not systematically captured by the routine overseas medical examination data collection process; when such conditions are present, routine processes give way to emergency response measures, which might include requirements for predeparture vaccinations, additional testing, isolation and quarantine, or suspension of processing and travel. This report focuses on TB, syphilis, gonorrhea, and Hansen's disease.

The overseas examinations are used as opportunities to offer additional, voluntary public health interventions. Major interventions offered to refugees include a vaccination program for most vaccine-preventable diseases and a presumptive treatment program for soil-transmitted helminthiasis, strongyloidiasis, schistosomiasis, and malaria infection.

FIGURE 1. CDC Electronic Disease Notification* system flow chart for new-arrival immigrants, refugees, and eligible others



Graphic courtesy of CDC

A postarrival TB examination is recommended by CDC for immigrants who have class A TB (and are admitted with a waiver) or class B TB. A comprehensive postarrival examination that includes a TB examination is recommended by CDC for all refugees and eligible others.

Overseas Medical Examination

In accordance with CDC Technical Instructions for Panel Physicians[7], the overseas medical examination for all applicants must include a medical history and physical examination. Additional required procedures and tests to further screen for TB, syphilis, gonorrhea, and Hansen's disease depend on age and location (Box 2). Panel physicians document their findings on the following DOS forms: DS-2054 Medical Examination for Immigrant or Refugee Applicant, DS-3030 TB Worksheet, DS-3025 Vaccination Documentation Worksheet, and DS-3026 Medical History and Physical Examination Worksheet. Medical examinations are valid for no more than 6 months. CDC ensures that these examinations fulfill the requirements through a robust quality assurance program that includes site visits, evaluations, and trainings.

Overseas Interventions for Refugees

Unlike immigrants, refugees are not required to receive vaccinations for admission to the United States, and many refugees might be undervaccinated when they receive their overseas medical examination, leaving them at risk for vaccine-preventable diseases. Refugees are required to demonstrate documentation of vaccinations when they adjust their status from refugee to immigrant, and they are required to apply for immigrant status after 1 year in the United States. To address this gap, CDC launched a voluntary vaccination program for U.S.-bound refugees in 2012[8]. The vaccination program is cofunded by CDC and DOS; the major implementing partner is the International Organization for Migration (IOM). The program provides refugees with the following vaccines, depending on age and eligibility: measles; mumps; rubella; hepatitis B; Haemophilus influenzae type B; pneumococcal conjugate vaccine; meningococcal conjugate vaccine with protection against serogroups A, C, W, and Y; diphtheria; tetanus; pertussis; and polio. Refugees typically receive these scheduled or catch-up vaccinations as recommended by the Advisory Committee on Immunization Practices at their initial overseas examination and, when logistically feasible, receive additional doses in each vaccine series before departure for the United States[8].

Except when contraindicated, refugees who receive their overseas examination in sub-Saharan Africa are offered albendazole for soil-transmitted helminth infections, ivermectin for Strongyloides stercoralis infection in countries where Loa loa is not endemic, praziquantel for schistosomiasis, and artemether-lumefantrine for Plasmodium falciparum in areas where malaria is endemic. In countries where L. loa is endemic, management of S. stercoralis is deferred until after arrival in the United States because of the risk for encephalopathy that might be associated with ivermectin treatment when L. loa infection is present. Refugees who receive their examinations in the Middle East, Asia, North Africa, Latin America, and the Caribbean are offered albendazole (for soil-transmitted helminths) and ivermectin (for strongyloidiasis) only. Refugees outside these areas, such as European countries and countries formerly in the Union of Soviet Socialist Republics, or those in areas with high infection rates for other parasitic infections (e.g., Plasmodium vivax), are offered specific treatment on a case-by-case basis.

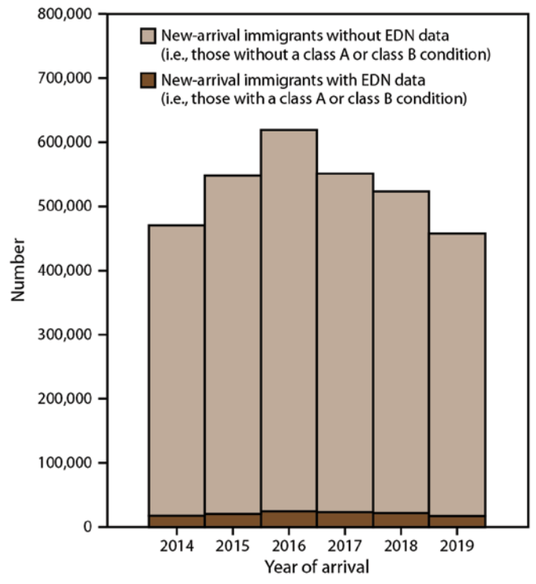
Postarrival Medical Examination in the United States

CDC recommends a TB examination for immigrants who have class A or B TB according to the overseas examination and recommends a comprehensive assessment that includes a TB examination for all refugees and eligible others[9]. Appropriate follow-up care in the United States can prevent progression from infection to disease or, if the disease has already developed or recurred since the overseas examination, allow rapid diagnosis and treatment, ultimately limiting spread within the United States. To facilitate outreach for the postarrival examination, CDC notifies state and local health departments whenever such persons arrive in the United States, typically within 1–9 days. U.S. clinicians affiliated with health departments conduct the postarrival examination, typically within 30–90 days. These voluntary follow-up examinations for newly arrived immigrants, refugees, and eligible others should not be confused with the required examination conducted by civil surgeons for adjustment-of-status immigrants who apply for lawful permanent residence status from within the United States.

Results

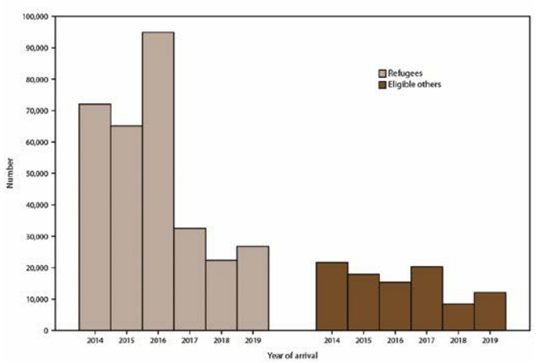
During 2014–2019, approximately 3.5 million persons entered the United States as new-arrival immigrants, refugees, or eligible others (Figures 2 and 3). Most (3.2 million) entered as new-arrival immigrants, averaging 528,252 annually (range: 457,930–619,100) (Figure 2). Each year, the largest proportions of immigrants were nationals of Mexico, the Dominican Republic, the People's Republic of China, the Philippines, Vietnam, India, Bangladesh, El Salvador, Haiti, and Pakistan, and the distribution of nationalities remained relatively constant over time (Supplementary Figure 1, https://stacks.cdc.gov/view/cdc/113063). Among all immigrants, 56% were nationals of these 10 countries. During the same period, 313,890 persons entered as refugees and 95,993 as eligible others (Figure 3). The number of refugees and eligible others who arrived each year declined from an average of 95,715 during 2014–2016 to an average of 40,912 during 2017–2019. Among refugees and eligible others, the largest proportions were nationals of Democratic Republic of Congo, Burma, Iraq, Cuba, Somalia, Bhutan, Syria, Ukraine, Iran, and Eritrea; however, the distribution of nationalities shifted markedly over time (Supplementary Figure 2, https://stacks.cdc.gov/view/cdc/113063).

FIGURE 2. Number of new-arrival immigrants* with and without overseas medical examination data collected by the Electronic Disease Notification system — United States, 2014–2019



Graphic courtesy of CDC

FIGURE 3. Number of refugees and eligible others* arriving per year — United States, 2014–2019



Graphic courtesy of CDC

Tuberculosis

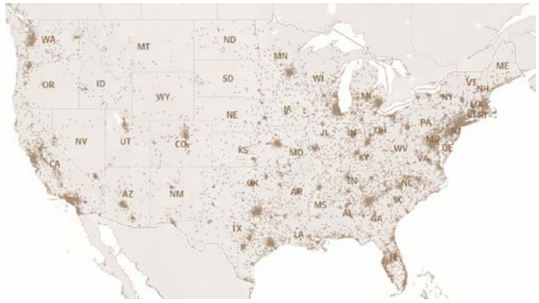
Among all 3.5 million immigrants, refugees, and eligible others who arrived in the United States during 2014–2019, the overseas examination identified 139,688 (3.9%) persons with class A or B TB, including five persons (0.0001% of entrants) with class A TB admitted with a waiver; 6,586 (0.2% of entrants) with class B0 TB, pulmonary; 94,533 (2.6% of entrants) with class B1 TB, pulmonary; and 38,023, mostly children, with class B2 TB, LTBI evaluation (Table 1). (Because testing for immune reactivity to M. tuberculosis is not required for most entrants, this report does not present the proportion of all entrants with class B2, LTBI evaluation.) The proportion of entrants with class A or B TB ranged from 3.7% to 4.1% by year and from 3.7% for immigrants, to 7.1% for refugees, to 1.4% for eligible others.

Notifications were sent for all 139,688 persons with class A or B TB to the relevant state or local health agency (Figure 4). This process facilitates a postarrival domestic follow-up examination. California received the most notifications (26.8%), followed by New York (8.7%) and Texas (8.3%). Among persons with class B0 TB, pulmonary, or with class B1 TB, pulmonary, the proportion with a complete postarrival TB examination reported to EDN within 1 year of arrival and ever, respectively, were 65.2% (first year) and 67.0% (ever) for immigrants, 74.8% and 75.7% for refugees, and 52.7% and 54.0% for eligible others (Table 2); the proportion reporting a complete postarrival examination within 1 year of arrival varied by state, with an overall proportion for immigrants, refugees, and eligible others ranging from 23.0% to 92.7% (Table 2).

Among children aged 2–14 years with class B2, LTBI evaluation, the proportion with a complete postarrival examination reported to EDN within 1 year of arrival and ever, respectively, were 55.9% (first year) and 58.4% (ever) for immigrants, 70.8% and 72.0% for refugees, and 45.9% and 47.9% for eligible others. The overall proportion for completion within 1 year of arrival by state ranged from 8.8% to 91.4% (Table 3). For all persons with class B TB, the proportion with a complete postarrival TB examination in EDN within 1 year of arrival was lowest in 2019 (Tables 2 and 3).

Among persons with a complete postarrival examination, culture-positive TB was diagnosed domestically in six persons (0.1%) identified overseas with class B0 TB, pulmonary, and for 458 (0.7%) persons identified with class B1 TB, pulmonary; among both groups together, the proportion with culture-positive TB diagnosed domestically remained constant over time, ranging from 0.6% to 0.8% during 2014–2019 (Table 2). Among children who were identified overseas with class B2, LTBI evaluation, and had a complete postarrival examination, culture-positive TB was diagnosed domestically among 11 children (0.05%), and LTBI was diagnosed among 10,223 (49.3%) (Table 3).

FIGURE 4. U.S. state and local health departments* that received notifications for arrival of immigrants, refugees, and eligible others† (N = 139,688) with class A or B tuberculosis§ — United States, 2014–2019



** U.S. territories and freely associated states are not shown.*

† New-arrival immigrants are persons who, while abroad, completed the application process for lawful permanent residency in the United States. Refugees are persons unable or unwilling to return to their country of nationality because of persecution, or a well-founded fear of persecution, resulting from their race, religion, nationality, membership in a particular social group, or political opinion. Eligible others are persons admitted from abroad, other than refugees, who are eligible for services from the Office of Refugee Resettlement (primarily parolees, Iraqi and Afghan special immigrant visa holders, and follow-to-join asylees).

Syphilis, Gonorrhea, and Hansen's Disease

During the study period, overseas evaluations for syphilis and gonorrhea were required for all persons aged ≥15 years. For children aged <15 years, evaluations were required when infection was suspected or a child had a history of infection. For syphilis, overseas laboratory test results were recorded for 94.9% of the 260,345 refugees and eligible others aged ≥15 years who arrived during 2014–2019. The proportion with results increased over time, reaching >99% among those examined in 2018–2019. A total of 1,025 syphilis cases were identified, a rate of 414.9 per 100,000 persons with recorded test results. A reporting requirement for syphilis stage was introduced in 2014. For refugees and eligible others who arrived after 2014, 54 primary or secondary syphilis cases (29.5 per 100,000 persons with test results) and 761 latent syphilis cases (415.3 per 100,000 persons with test results) were identified overseas; the latter included 248 cases of unknown duration.

Rates for primary and secondary syphilis were highest among persons aged ≥30 years, and rates for latent syphilis increased with each age group (Table 4). For gonorrhea, a requirement for laboratory testing was introduced in 2016, and reliable data are only available for those examined in 2018 or later. Among 35,653 refugees and eligible others aged ≥15 years examined in 2018–2019, a gonorrhea test result was documented for 98.3%; 131 cases of gonorrhea were identified (373.7 per 100,000 persons with test results), and rates were highest among persons aged 15–34 years. Persons of all ages are screened for Hansen's disease during their overseas medical examination; among all 409,883 refugees and eligible others who arrived during 2014–2019, a total of 25 had a diagnosis of Hansen's disease (6.1 per 100,000 persons examined).

Vaccination Program and Presumptive Treatment for Refugees

CDC's vaccination program for refugees began in December 2012 in two countries, Thailand and Nepal. By 2014, the program operated in 39 of 89 countries where overseas medical examinations for refugees were performed. Among all refugees who arrived that year, EDN data showed that first- and second-dose coverage with measles-containing vaccine for 66,727 eligible refugees (those born after 1956, who were aged at least 1 year before departing for the United States, and titers, if available, do not indicate immunity) were 49% and 41%, respectively.

By 2019, the vaccination program had expanded to all 73 countries where examinations for 22,142 refugees were performed and for that calendar year achieved first-dose coverage of 96% and second-dose coverage of 80%. Among 846 eligible refugees who did not receive a first dose overseas, 17% were pregnant, 15% had another contraindication, 31% were subject to local vaccine shortages, and 6% did not have enough time to get vaccinated. Live virus vaccines, such as measles vaccine, are not routinely administered within 28 days of departure for the United States to avoid interference with any live vaccines or tests of immune response for M. tuberculosis antigen testing administered shortly after arrival in the United States (16).

CDC's presumptive treatment program for soil-transmitted helminthiasis, strongyloidiasis, schistosomiasis, and malaria infection varies by country. In populations for whom treatment was recommended, the proportion with documented treatment was 96% for albendazole, 79% for ivermectin (increasing to 84% when countries in which ivermectin is not licensed were excluded), 87% for praziquantel, and 93% for artemether-lumefantrine.

cdc.gov

Tuberculosis Cases Remain Highest at U.S. Border

Awareness and testing for refugees and health professionals is imperative to prevent transmission of infection to others

According to the Texas department of State Health Services, the rate of tuberculosis (TB) on the Texas-Mexico border has typically been higher than the rest of the state. Being born in a foreign country is a risk factor for TB and a large proportion of the population living on the Texas-Mexico border was born in Mexico or Central America. Higher than average rates of TB are also found in Houston and Dallas, where a large proportion of the population is also foreign-born.

The demographics of persons diagnosed with TB on the Texas-Mexico border are similar to the state overall. Persons with TB in the Texas-Mexico border region tend to be less than 45 years old and are overwhelmingly Hispanic (93%), reflecting the demographics of the local general population. Diabetes, foreign birth, and incarceration are more common risk factors for persons with TB on the Texas-Mexico border, whereas homelessness is less common.

Certain tuberculosis outcomes for persons living in the Texas-Mexico border region were slightly worse than the state overall. While slightly fewer persons (5%) died prior to therapy completion in the border region compared to the state overall (6%)more of persons living in the border region died within a month of diagnosis (3%) compared to cases statewide (2%). Three percent of cases were lost to follow up in the border region compared to two percent statewide. About two percent of cases were diagnosed after death, indicating a missed opportunity for screening, detection, and treatment. Diagnoses after death may also indicate a missed opportunity to prevent transmission of TB infection to others.

The CDC's Guidance for Screening for Tuberculosis Infection and Disease during the Domestic Medical Examination for Newly Arrived Refugees focuses on the following key points:

- As part of the domestic screening, all overseas medical records should be reviewed, a thorough medical history obtained, and a physical examination completed.
- All refugee applicants (aged ≥2 years) must undergo evaluation overseas for tuberculosis (TB) and are assigned one or more TB classifications prior to departure. Overseas TB screening results, treatment, and classifications are documented on the US Department of State (DS) forms.

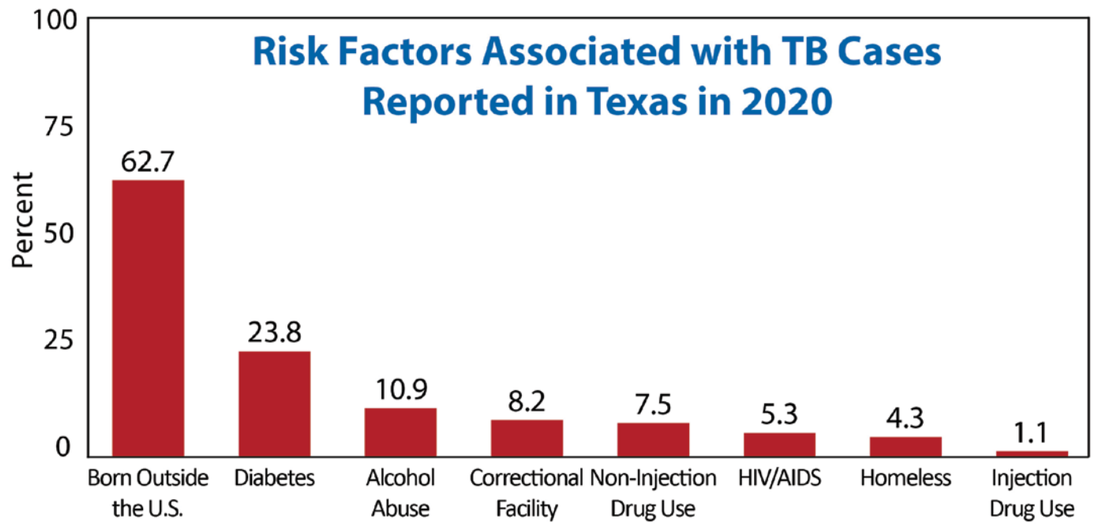


Chart courtesy of the Texas Department of State Health Services

- Domestic TB evaluation for newly arrived refugees from endemic countries:
  - For children aged 2–14 years:
    - — If Interferon Gamma Release Assay (IGRA) was negative overseas (within the last 6 months), and there are no signs or symptoms of TB disease upon physical examination, no further domestic evaluation is needed.
    - — If the overseas IGRA was negative but performed ≥6 months prior to the domestic examination, repeat IGRA.
    - — Treatment for latent tuberculosis infection (LTBI) should be considered after TB disease is ruled out for those with positive IGRA results, unless TB disease or LTBI treatment was completed prior to arrival.
  - For children aged <2 years, a tuberculin skin test (TST) is recommended (if not previously treated for LTBI or TB disease).
  - For refugees aged ≥15 years:
    - — If IGRA was not done overseas or a negative IGRA was documented >6 months prior, an IGRA is recommended at the domestic examination.
    - — If overseas or domestic IGRA is positive, LTBI treatment should be considered after TB disease is ruled out (if not previously treated for LTBI or TB disease).
  - Any refugee, regardless of country of origin, with signs or symptoms of TB disease should undergo clinical evaluation for TB disease
- Differentiating between LTBI and TB Disease (Pulmonary)

All refugees, including those classified with a TB condition overseas, should receive a comprehensive domestic medical screening within 90 days of arrival. The goal of the domestic screening for TB is to find persons with LTBI, in order to facilitate prompt treatment and control, and to find persons who may have developed TB disease since the overseas medical examination.

Testing Newly Arrived Refugees for TB Infection and Disease

The overseas medical exam is universal for all refugees. Results of overseas TB testing and treatment should be available to domestic clinicians for review for all refugee arrivals from TB endemic countries.

For children 2 to 14 years of age coming from endemic countries (TB incidence rate of ≥20 cases per 100,000 population), an IGRA result should be available. If the IGRA was negative and performed <6 months before departure, and if the child has no signs or symptoms of TB disease upon physical examination, no further evaluation is needed. Additionally, if the IGRA was positive and the child completed TB disease or LTBI treatment prior to the domestic examination and has no signs or symptoms of

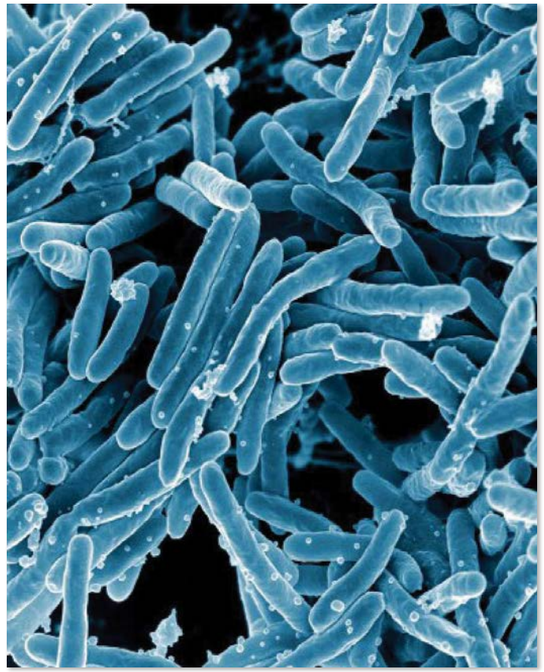


Photo courtesy of NIH

TB disease upon physical examination, no further evaluation is needed. If the IGRA was negative but performed ≥6 months prior to the domestic examination, a repeat IGRA should be performed. For children aged <2 years from endemic countries, LTBI testing is recommended, if not previously treated for TB disease or LTBI. Currently, TST is the preferred test for children age <2 years. Skin testing and interpretation should be done in accordance with the ATS/CDC/IDSA Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Childrenexternal icon.

Refugees >15 years of age are universally screened with a CXR prior to arrival in the US. Refugees >15 years of age who have clinical signs or symptoms of TB disease, or have a positive CXR, or who are HIV positive, will have had three sputum smears and three sputum cultures performed prior to arrival.

If they are diagnosed with TB disease, they receive full DOT prior to arrival. If a refugee ≥15 years has LTBI diagnosed prior to arrival but has not received LTBI treatment, they should be offered treatment if they have no current no signs or symptoms suggestive of TB disease and no contraindications to treatment. A refugee aged >15 years who had a normal CXR prior to departure should be offered an IGRA if —

- overseas IGRA was not performed
- overseas IGRA results are unavailable or
- overseas IGRA screening was performed >6 months prior and results were negative.

Any new arrival, regardless of country of origin, with signs or symptoms of TB should undergo clinical evaluation for TB disease. CDC treatment guidelines call for clinicians to not only prescribe an appropriate regimen (length of course of treatment and treatment regimen), but also ensure adherence to the regimen until treatment is completed. TB disease should be diagnosed and treated in consultation with the public health department and TB medical experts.

cdc.gov

Despite being preventable and treatable, TB remains the world's leading infectious disease killer, taking the lives of 1.4 million people in 2019 alone. Two billion people — one fourth of the world's population — are infected with the TB bacteria, with more than 10 million becoming ill with active TB disease each year. In 2019, 1.2 million children fell ill with TB globally and 465,000 people fell ill with drug-resistant TB. TB knows no borders. It is present in all countries around the world and in all age groups.

Although the United States has reported record low cases, too many people still suffer from TB disease in this country. Up to 13 million people in the United States have latent TB infection, and without treatment, are at risk for developing TB disease in the future. CDC's work in the United States supports a dual approach to find and treat active TB disease and test for and treat latent TB infection to prevent progression to disease. Expanded testing and treatment for latent TB infection, better diagnostics, and strong partnerships both domestic and global, are needed to turn TB elimination into a reality.

Looking ahead, CDC is engaging private and public primary healthcare providers who represent the front line in the fight against latent TB infection. CDC is working to make testing for latent TB infection a routine part of primary care for patients at higher risk of TB disease, encouraging healthcare providers to use newer TB blood tests to screen for latent TB infection and prescribe shorter treatments for latent TB infection to prevent the development of TB disease.

NIAID Pandemic Preparedness Plan Targets 'Prototype' and Priority Pathogens

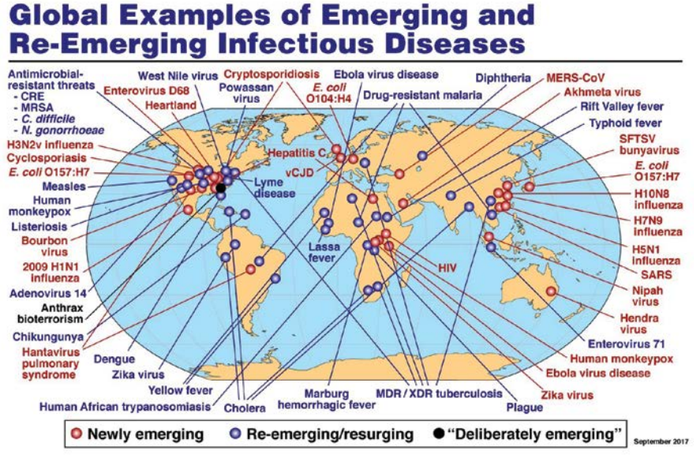
Preemptive Approach Designed to Identify Viral Threats Before they Emerge

As the global COVID-19 pandemic continues into its third year, the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, is focusing on preparing for a range of other viral threats that could cause a public health emergency. For decades, NIAID has launched major research responses and developed medical countermeasures to combat multiple emerging infectious diseases, including HIV/AIDS, SARS-CoV-1, Middle East respiratory syndrome coronavirus (MERS-CoV), Ebola virus, Zika virus, and SARS-CoV-2.

According to NIAID's new Pandemic Preparedness Plan, the institute will direct its preparedness efforts on two fronts. First, researchers will identify "prototype pathogens" — viruses within viral families with the potential to cause significant human disease. Knowledge gained from studying prototype pathogens will also build a framework for a rapid research and product development response for other viruses within that virus family should an outbreak occur. For example, NIAID's earlier research on SARS-CoV-1 and MERS-CoV informed rapid vaccine development for SARS-CoV-2 in 2020. The plan's second key research focus is on priority pathogens — viruses already known to be capable of causing significant human illness or death, such as Zika virus.

NIAID aims to support critical basic and preclinical studies to characterize these prototype and priority pathogens, including understanding viral biology and structure, host-immune responses, mechanisms of immune evasion, disease pathogenesis and animal models of disease. NIAID will apply this knowledge to conduct translational and clinical research to develop diagnostics; therapeutics, including antivirals, monoclonal antibodies, and broad-spectrum approaches; and vaccines. These efforts are designed to shorten timelines between pathogen emergence and authorization/approval of candidate products.

NIAID's approach to pandemic preparedness. Graphic courtesy of NIAID



Graphic courtesy of NIAID

The institute's comprehensive preparedness efforts will also include novel epidemiology and pathogen discovery programs, pre-clinical and clinical infrastructure capacity, technology enhancements to hasten therapeutic and vaccine development, and a robust and coordinated communication structure, according to the plan. NIAID will continue to collaborate with partners in the U.S. and foreign governments, the biopharmaceutical industry, and international organizations on its preparedness efforts.

The new plan was informed by a November 2021 workshop NIAID hosted to facilitate discussions with the scientific community about the development of a pandemic preparedness strategy and prioritizing prototype pathogens within viral families of concern. Moving forward, NIAID will continue to engage the scientific community and U.S. and global partners to ensure preparedness planning efforts are collaborative, integrated, and aligned with current scientific research.

niaid.nih.gov

Most U.S. Rabies Infections Caused by Bats

By Peter J. Costa, MPH, MCHES, AVES (Hon), U.S. Medical Affairs Regional Lead, Bavarian Nordic

Rabies is a deadly, but preventable, viral disease that infects the brain[1]. Rabies virus is maintained in animal populations and is most often transmitted to humans through the bite of a rabid animal[2]. After exposure, immediate medical attention — known as rabies post-exposure prophylaxis (PEP) — is required.

Rabies is nearly always fatal if people do not receive PEP before symptoms start. Around the world, an estimated 59,000 people die from rabies every year — most often following an untreated bite from a rabid dog. In the U.S., human rabies deaths are far less common, averaging 1-3 cases annually, even though 30,000-60,000 people come into contact with potentially rabid animals each year and require PEP[4].

In the U.S., wild animals, and especially bats, are most responsible for transmitting rabies to humans. Rabid bats have been reported in every state except Hawaii and bats are the leading cause of human rabies deaths in the U.S.[5].

During 2021, five people died from rabies in the U.S., the most since 2011, when six people succumbed to the fatal illness[3,4]. Four out of the five rabies deaths in 2021 were attributed to bats. Three of those cases occurred during September 28-November 10, 2021. In each case, the patients recognized they had been in contact with a bat, but none of the three individuals sought medical attention.

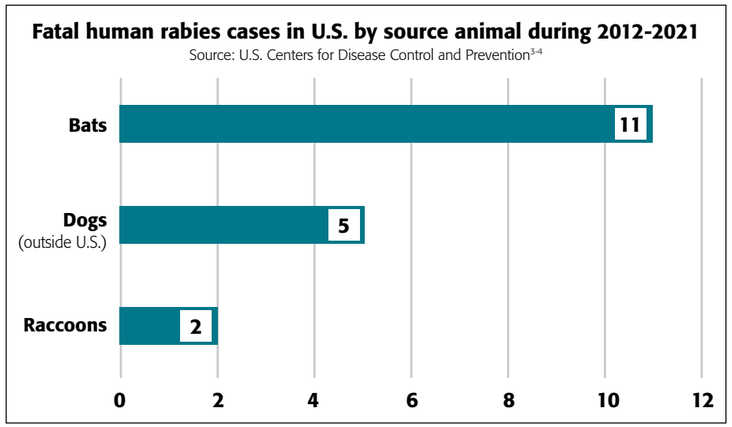
Oftentimes people do not realize the risk for rabies after exposure to bats. Yet, since the 1960s, approximately 70% of people who died from rabies in the U.S. were infected by bats[6]. Unlike bites from larger wild animals such as raccoons, skunks and foxes, bat bites can be very small, and some people may minimize the severity of the exposure or not even realize that they have been bitten.

This is an anterior view of the face of a Myotis lucifugus, or little brown bat, found in Trenton, New Jersey. M. lucifugus is a member of the family Vespertilionidae, and is prevalent throughout North America. These mammals seldom become aggressive when rabid, and therefore, rarely transmit rabies to humans. Photo courtesy of CDC

Bats serve many important roles in our ecosystems and most bats do not have rabies, but bats are responsible for most human cases of rabies in the U.S. While you can't tell if a bat has rabies just by looking at it, rabid bats may exhibit none, some or all of the following behaviors: daytime activity; inability to fly; flopping on ground; unusual sounds such as hissing; and no fear of people.

Rabies is one of the deadliest diseases in the world — killing 99.9% of people who become infected. It is critical that people are aware of the potential rabies risk posed by bats and seek prompt medical treatment if they suspect they've been bitten or exposed to rabies. Bats are the most commonly reported rabid animal in the U.S. Protect yourself by staying away from bats and teaching others, especially children, to never touch a bat.

Anyone who suspects they've been bitten or otherwise exposed to rabies should immediately and thoroughly clean any wounds with soap and water and seek medical attention right away. Health care professionals will evaluate the exposure to determine if rabies post-exposure prophylaxis is needed. When administered promptly and properly, rabies post-exposure prophylaxis is essentially 100% effective at preventing rabies in humans[1].



Bats are the leading cause of human rabies deaths in the U.S. followed by exposure to dogs in certain areas of the world where rabies in dogs is still a major problem and access to post-exposure prophylaxis may be limited. Travelers to countries where rabies is widespread should avoid contact with animals and consult a healthcare provider about the possibility of receiving rabies pre-exposure vaccination before traveling abroad[7].

Peter Costa is the U.S. Medical Affairs Regional Lead for Bavarian Nordic, a rabies vaccine manufacturer. Peter is a public health practitioner, master certified health education specialist and an honorary member of the American Veterinary Epidemiology Society. In addition to his work with Bavarian Nordic, Peter volunteers with the non-profit One Health Commission-Bat Rabies Education Team and Rabies in the Americas Committee (RITA). Peter is a co-founder and previous coordinator of the annual World Rabies Day observance founded in 2007 and held each year on September 28th to raise global awareness about rabies prevention. Peter's true rabies passion is the public health management of humans at risk, with particular emphasis on mass awareness and education strategies. Correspondence to peco@bavarian-nordic.com

This image depicts a horde of unidentified bats, an animal known to be a possible carrier of the rabies virus. Photo courtesy of CDC

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US-RAB-2200004. February 2022

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NIH Announces Winners of Data Challenge to Identify Risk Factors for First-time Pregnancies

The winners of the National Institutes of Health's Decoding Maternal Morbidity Data Challenge were announced in conjunction with the White House "day of action" on maternal health. Twelve prizes were awarded to seven winners who proposed innovative solutions to identify risk factors in first-time pregnancies. Without a prior pregnancy for comparison, it is difficult to identify risks for adverse pregnancy outcomes. Early detection of these risks can help reduce pregnancy complications and prevent maternal deaths.

"Any maternal death is one too many," said Diana W. Bianchi, MD, director of NIH's Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which administered the challenge. "A healthy pregnancy and childbirth should be a given, but sadly, it's not. Understanding and reducing pregnancy-related complications and deaths — or maternal morbidity and mortality — is a high priority for NIH."

Diana W. Bianchi, MD, is the director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development and head of the Prenatal Genomics and Therapy Section for the Medical Genetics Branch at NHGRI. Photo courtesy of Diana Bianchi and Youtube

In the United States, more than 700 women die each year from pregnancy complications or giving birth, according to the Centers for Disease Control and Prevention. Another 50,000 women experience life-threatening complications that are considered "near misses" for maternal death, sometimes causing serious, long-term health problems. The CDC estimates that Black women are three times more likely to die from a pregnancy-related cause than white women. Women over age 35 years or those residing in rural areas are also at higher risk.

Last year, NIH spent an estimated $224 million in research funding to prevent maternal morbidity and mortality. While most of these funds went toward traditional funding mechanisms, challenges offer unique opportunities to stimulate ideas and solutions. The Decoding Maternal Morbidity Data Challenge prizes totaled $400,000. Seven prizes of $50,000 were awarded for innovation, and five additional prizes of $10,000 were awarded for addressing health disparities.

All the proposals analyzed participant data from NICHD's Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b), a racially, ethnically and geographically diverse sample of people who are pregnant for the first time. NuMoM2b was established in 2010 and has compiled data on more than 10,000 pregnant women, including research data beginning in the sixth week of pregnancy and continuing through delivery.

"The winning teams developed methods to analyze the data, accurately flagging cases that were high-risk for complications," said NICHD's Maurice Davis, DHA, who managed the challenge. "These computational methods can now be used to analyze additional data from other pregnancies. These solutions have the potential to make a real difference and save lives."

The team leads for each of the winning proposals are as follows (asterisks denote winners of both prize categories):

Nicole Carlson, PhD*
Emory University, Atlanta

Ali Ebrahim, PhD
Delfina, San Francisco

Britnee Johnston*
Johnston and Company, LLC,
Salt Lake City

Monica Keith, PhD*
University of Washington,
Seattle

Yaping Li
Feng Ya, LLC,
Watkinsville, Georgia

Ainesh Pandey*
IBM Data Science and
AI Elite, San Francisco

Ansaf Salleb-Aouissi, PhD
Columbia University,
New York City

nih.gov

U.S. Surgeon General Issues Advisory on Youth Mental Health Crisis Further Exposed by COVID-19 Pandemic

U.S. Surgeon General Dr. Vivek Murthy issued a new Surgeon General's Advisory to highlight the urgent need to address the nation's youth mental health crisis. As the nation continues the work to protect the health and safety of America's youth during this pandemic with the pediatric vaccine push amid concerns of the emerging omicron variant, the U.S. Surgeon General's Advisory on Protecting Youth Mental Health outlines the pandemic's unprecedented impacts on the mental health of America's youth and families, as well as the mental health challenges that existed long before the pandemic.

The Surgeon General's advisory calls for a swift and coordinated response to this crisis as the nation continues to battle the COVID-19 pandemic. It provides recommendations that individuals, families, community organizations, technology companies, governments, and others can take to improve the mental health of children, adolescents and young adults.

The pandemic added to the pre-existing challenges that America's youth faced. It disrupted the lives of children and adolescents, such as in-person schooling, in-person social opportunities with peers and mentors, access to health care and social services, food, housing, and the health of their caregivers.

"Mental health challenges in children, adolescents, and young adults are real and widespread. Even before the pandemic, an alarming number of young people struggled with feelings of

Vice Admiral Vivek H. Murthy, MD, MBA, U.S. Surgeon General Department of Health and Human Services. Photo courtesy of HHS

helplessness, depression, and thoughts of suicide — and rates have increased over the past decade." said Surgeon General Vivek Murthy. "The COVID-19 pandemic further altered their experiences at home, school, and in the community, and the effect on their mental health has been devastating. The future wellbeing of our country depends on how we support and invest in the next generation. Especially in this moment, as we work to protect the health of Americans in the face of a new variant, we also need to focus on how we can emerge stronger on the other side. This advisory shows us how we can all work together to step up for our children during this dual crisis."

Before the COVID-19 pandemic, mental health challenges were the leading cause of disability and poor life outcomes in young people, with up to 1 in 5 children ages 3 to 17 in the U.S. having a mental, emotional, developmental, or behavioral disorder.

Additionally, from 2009 to 2019, the share of high school students who reported persistent feelings of sadness or hopelessness increased by 40%, to more than 1 in 3 students.

Suicidal behaviors among high school students also increased during the decade preceding COVID, with 19% seriously considering attempting suicide, a 36% increase from 2009 to 2019, and about 16% having made a suicide plan in the prior year, a 44% increase from 2009 to 2019. Between 2007 and 2018, suicide rates among youth ages 10-24 in the U.S. increased by 57%, — PDF and early estimates show more than 6,600 suicide deaths — PDF among this age group in 2020.

The pandemic added to the pre-existing challenges that America's youth faced. It disrupted the lives of children and adolescents, such as in-person schooling, in-person social opportunities with peers and mentors, access to health care and social services, food, housing, and the health of their caregivers. The pandemic's negative impacts most heavily affected those who were vulnerable to begin with, such as youth with disabilities, racial and ethnic minorities, LGBTQ+ youth, low-income youth, youth in rural areas, youth in immigrant households, youth involved with the child welfare or juvenile justice systems, and homeless youth.

This Fall, a coalition of the nation's leading experts in pediatric health declared a national emergency exit disclaimer icon in child and adolescent mental health.

The Surgeon General's Advisory on Protecting Youth Mental Health outlines a

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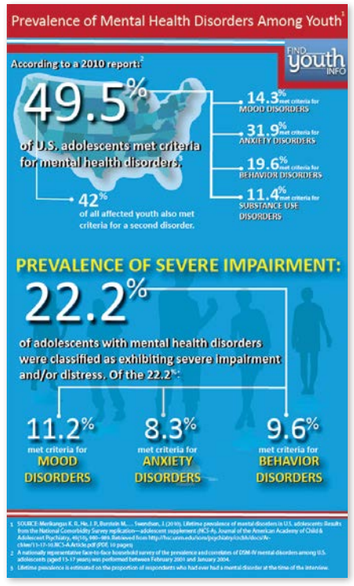


Photo courtesy of youth.gov

series of recommendations to improve youth mental health across eleven sectors, including young people and their families, educators and schools, and media and technology companies.

Topline recommendations include:

- Recognize that mental health is an essential part of overall health.
- Empower youth and their families to recognize, manage, and learn from difficult emotions.
- Ensure that every child has access to high-quality, affordable, and culturally competent mental health care.
- Support the mental health of children and youth in educational, community, and childcare settings. And expand and support the early childhood and education workforce.
- Address the economic and social barriers that contribute to poor mental health for young people, families, and caregivers.
- Increase timely data collection and research to identify and respond to youth mental health needs more rapidly. This includes more research on the relationship between technology and youth mental health, and technology companies should be more transparent with data and algorithmic processes to enable this research.

Surgeon General's Advisories are public statements that call the American people's attention to a public health issue and provide recommendations for how it should be addressed. Advisories are reserved for significant public health challenges that need the American people's immediate attention.

hhs.gov

Brain Activity Patterns after Trauma May Predict Long-term Mental Health

Study shows link between post-trauma brain activity and symptoms of anxiety, PTSD six months later.

The way a person's brain responds to stress following a traumatic event, such as a car accident, may help to predict their long-term mental health outcomes, according to research supported by the National Institute of Mental Health (NIMH), part of the National Institutes of Health. The research, published in the American Journal of Psychiatry, is part of the NIMH-funded AURORA study, a large-scale, multisite study that followed more than 3,000 people for up to a year after exposure to a traumatic event.

Evidence from previous studies suggests that it's common for people to show a wide range of responses after a traumatic experience, such as a natural disaster or serious accident. One person may show initial symptoms that diminish naturally over time, while another may have long-lasting symptoms that make it difficult to carry out everyday activities. These different responses do not fall neatly into existing diagnostic categories and, although there are known risk and resilience factors associated with mental health outcomes, researchers aren't yet able to predict how a specific person will fare after experiencing a traumatic event.

Using a variety of neurobiological, behavioral, and self-report measures, the AURORA study researchers hope to develop a comprehensive picture of the factors that play a role in trauma survivors' mental health over time. To help advance this effort, AURORA study data will be made available to the broader research community through the NIMH Data Archive.

As part of the study, Jennifer Stevens, PhD, of Emory University in Atlanta,

Jennifer Stevens, PhD, Assistant Professor Psychiatry and Behavioral Sciences. Photo courtesy of Emory University

led an investigation of post-trauma brain activity in an initial group of 69 AURORA participants who were seen in an emergency department following a car crash. Stevens and colleagues hypothesized that different patterns of stress-related brain activity may predict participants' long-term mental health symptoms across a range of diagnoses.

Two weeks after the accident, the participants had their brain activity measured via functional MRI while they completed a series of standard computer-based tasks. The tasks assessed their brain activity in response to social threat cues, reward cues, and situations that required them to inhibit a response.

Over the next six months, the participants also completed digital surveys in which they self-reported symptoms of post-traumatic stress disorder (PTSD), depression, dissociation, anxiety, and impulsivity.

Analyses of the participants' brain activity data revealed four distinct profiles:

- Reactive/disinhibited: High activity related to both threat and reward; little activity related to response inhibition
- Low-reward/high-threat: High activity related to threat; low activity related to reward
- High-reward: No activity related to threat; little activity related to response inhibition; high activity related to reward
- Inhibited: De-activation related to threat; some activity related to inhibition; low activity related to reward

The researchers then performed the same analyses with a separate group of 77 AURORA participants who also were seen in an emergency department following exposure to a range of traumatic events not limited to car crashes. In this group, they found evidence for three of the four profiles: reactive/disinhibited, low-reward/high-threat, and inhibited. These profiles were not correlated with other demographic, health-related, trauma-related, or site-specific characteristics.

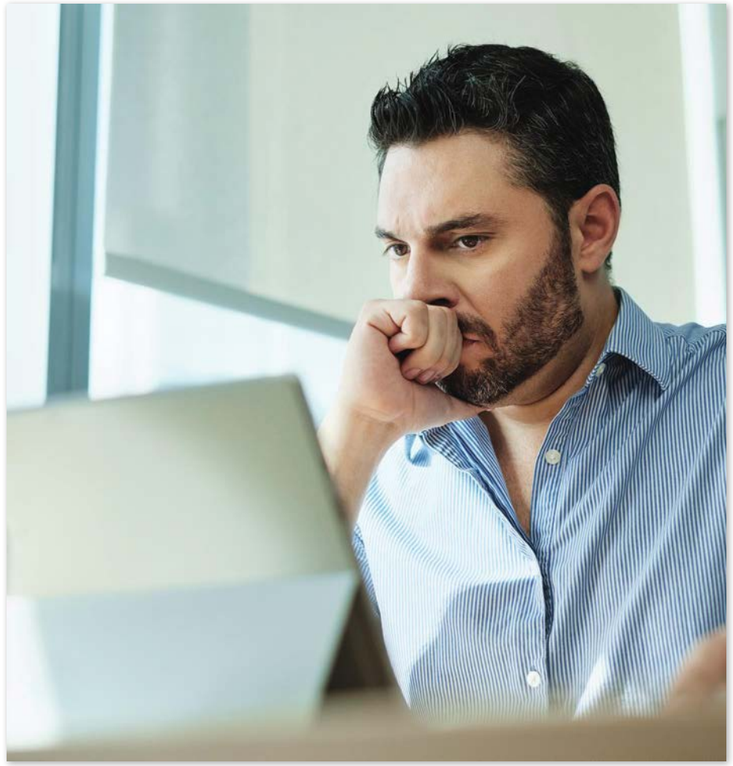
Looking at participants' brain activity profiles in relation to their mental health outcomes, Stevens and co-authors found that participants with the reactive/disinhibited profile — those who showed high activity related to both threat and reward — reported higher levels of symptoms

of both PTSD and anxiety over the six-month follow-up period compared with the other profiles.

The researchers found no association between any of the brain activity profiles and other mental health outcomes, such as symptoms of depression, dissociation, or impulsivity.

The link between high reward reactivity (as part of the reactive/disinhibited profile) and long-term symptoms was unexpected, as previous studies indicated an association between low reward reactivity and post-trauma PTSD and depression. The divergent findings could be explained by the fact that reactivity to reward and threat are rarely examined together in trauma-related studies. The researchers suggest that reward reactivity warrants greater attention in future studies as a potential risk factor for stress-related symptoms following trauma.

These findings are preliminary and additional research with larger samples will be needed to confirm and refine these brain-based profiles. However, these initial findings suggest that the profiles could provide meaningful information about a person's vulnerability to stress after experiencing a traumatic event. Establishing reliable, predictive profiles of stress response could improve clinical care, helping providers deliver effective interventions that are tailored to trauma survivors' individual needs and circumstances.



About 19 percent of U.S. adults have an anxiety disorder in any given year, and an estimated 31 percent have an anxiety disorder at some time in their lives. Anxiety disorders are generally treated with psychotherapy, medication, or both. Photo courtesy of NIH credit Getty Images

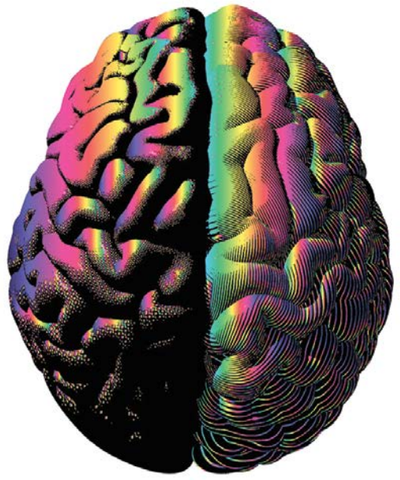


Photo courtesy of NIH

Grants: MH110925 (NIMH and U.S. Army Medical Research and Material Command), MH119603, MH118467

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NIH-funded Study Could Help Improve Deep Brain Stimulation Therapy for OCD

Study sheds light on potential for long-term, at-home use of deep brain stimulation as a treatment for neuropsychiatric disorders

In a small study, researchers funded by the National Institutes of Health captured more than 1,000 hours of brain recordings from patients with OCD in the clinic and at home. These data are a key first step towards designing improved deep brain stimulation (DBS) treatments for neuropsychiatric disorders.

DBS has shown great promise for improving the lives of people living with neurological disorders such as Parkinson's disease, and is now gaining traction for treating psychiatric conditions such as obsessive-compulsive disorder (OCD). The study is published in Nature Medicine and funded through the NIH Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative.

"By combining at-home and in-clinic brain recordings, this study could aid in the development of adaptive DBS treatments, which could be transformative for people living with OCD," said John J. Ngai, PhD, director of the NIH BRAIN Initiative. "This kind of far-reaching, high-impact work is precisely what the BRAIN Initiative was established to support."

Researchers, led by David Borton, PhD, associate professor of biomedical engineering at Brown University, Providence, Rhode Island, and Wayne K. Goodman, MD, the DC and Irene Ellwood Chair in Psychiatry at Baylor College of Medicine, Houston, collected brain recordings from three patients who were already receiving DBS treatment for OCD.

These recordings occurred in the clinic, during teletherapy sessions, and during normal life activities at home. These data will be used to correlate specific brain patterns with OCD symptoms, with the goal being the identification of neural signatures and related behaviors that predict the onset of symptoms and that can be used to further refine DBS treatment. The at-home component to the recordings is a particularly important advancement, since that is the environment where patients are being exposed to the triggers that affect their daily lives.

OCD and other neuropsychiatric disorders are challenging to treat with DBS because the symptoms fluctuate over time. Unlike motor disorders, such as Parkinson's disease that are commonly improved with DBS, the symptoms of OCD come and go over time and can be triggered by the person's environment.

"Currently, DBS therapy for OCD involves implanting the electrodes, turning on the stimulation, and then fine-tuning that stimulation as best as possible in the clinic," said Dr. Borton. "But because symptoms can be triggered by many factors, the clinician is tuning the DBS system for the patient at that moment in the clinic, but their needs could change significantly once they leave the clinic."

Another enormous challenge is the current lack of biomarkers — distinct and measurable changes in brain activity — for OCD symptoms. In addition, changes in symptoms in response to DBS for neuropsychiatric disorders can take weeks or even months to occur once treatment begins. This means that clinicians programming the DBS system must rely on secondary behavioral changes such as a positive affect response — patients feel happier or more talkative when stimulation is turned on.

"Changes in affect can tell us that we are stimulating the right area of the brain, but not necessarily that the stimulation itself is ideally tuned," said Dr. Goodman.

The researchers in this study aimed to tackle these challenges by using a technology similar to what had been previously used by BRAIN Initiative investigators in patients with Parkinson's disease.

In the current study, brain recordings were taken from the same electrodes responsible for delivering the DBS therapy and time-synched to EEG, other physiological recordings, and facial changes when recorded in the clinic; to efforts to evoke symptom responses during teletherapy sessions; and to self-reported symptoms during everyday life and during prescribed tasks at home.

By combining these diverse data sets, the researchers were able to begin identifying candidate neurological signatures for OCD, such as brain activity changes that occurred over time in correlation with clinical scores for OCD symptoms. Going forward, the researchers plan to tweak the stimulation in response to the candidate biomarkers to confirm whether they can be used to impact the onset of symptoms.

In addition, recordings from the cortical surface of patients, similar to what was done in the study of Parkinson's disease, will be added to provide an additional layer of information.

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HHS Seeks Public Comments to Advance Equity & Reduce Disparities in Organ Transplantation, Improve Life-Saving Donations, and Dialysis Facility Quality of Care

This effort builds upon the recent Organ Procurement Organizations' Conditions for Coverage (CfCs) final rule to help thousands of patients on waitlists

Today, the U.S. Department of Health and Human Services, through the Centers for Medicare & Medicaid Services (CMS) issued a Request for Information (RFI) to solicit stakeholder and public feedback that will be used to inform potential changes and future rulemaking to improve the organ transplantation system and seek to enhance the quality of life of those living with organ failure.

This is part of the Biden-Harris Administration's ongoing efforts to improve the health outcomes of the more than 106,000 people who are waiting to receive a life-saving or life-enhancing organ transplant.

CMS is focused on identifying potential system-wide improvements that would increase organ donations, improve transplants, enhance the quality of care in dialysis facilities, increase access to dialysis services, and advance equity in organ donation and transplantation.

Critical to these system-wide improvements is the close, collaborative relationship among Organ Procurement Organizations (OPOs), donor hospitals, transplant programs, and End-Stage Renal Disease (ESRD) facilities to ensure that organs are successfully recovered and transplanted. These providers and suppliers are integral to the nation's transplant ecosystem and the health of patients across the nation.

Graphic courtesy of organdonor.gov

Chiquita Brooks-LaSure is the Administrator for the Centers for Medicare and Medicaid Services (CMS). Photo courtesy of CMS.

"Today's announcement supports the President's Executive Orders to advance health equity and improve health outcomes for people in need of a life-saving transplant and dialysis," said Health and Human Services Secretary Xavier Becerra. "We want to hear from diverse stakeholders, especially the patients and their families. Your feedback is essential to our work in ensuring equal access to vital resources."

Communities of color have much higher rates of high blood pressure, diabetes, obesity, and heart disease, all of which increase the risk for kidney disease.

Black Americans are almost four times more likely, and Latinos are 1.3 times more likely, to have kidney failure compared to White Americans.

Despite the higher risk, data shows that Black and Latino patients on dialysis are less likely to be placed on the transplant waitlist and have a lower likelihood of transplantation. Because of these stark inequities, CMS' RFI asks the public for specific ideas on advancing equity within the organ transplantation system, particularly on potential changes to the health and safety standards for transplant programs, ESRD facilities, and OPO operations.

"Organ donation is a precious gift, and we owe it to recipients, donors, those awaiting organs, and their loved ones to ensure our transplantation system is safe, efficient, and equitable," said CMS Administrator Chiquita Brooks-LaSure.

"We are seeking input on ways to improve organ donation and transplantation and are committed to engaging all stakeholders throughout our policy development process. This effort is extremely important for supporting organ transplants for communities of color, individuals with disabilities, and other historically underserved populations."

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NIH-supported Study Suggests Alternative to Race-based Kidney Function Calculations

Alternate lab test shows comparable accuracy, non-biased results

In a study supported by the National Institutes of Health, researchers propose changing a key measure in kidney disease diagnosis and treatment to eliminate the use of race as a variable, providing a non-biased kidney function test that does not compromise accuracy. The study suggests use of a blood lab test called cystatin C, which does not vary by a person's race, to replace the current lab test called creatinine, which does. The findings come from a detailed analysis of data from the Chronic Renal Insufficiency Cohort (CRIC) Study, a nationwide longstanding study funded by NIH's National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The results are published in the New England Journal of Medicine.

Health care providers use estimated glomerular filtration rate, or eGFR, calculations as a primary diagnostic tool to learn how well a person's kidneys function and to classify the severity of their disease, from mild loss of kidney function to end-stage kidney disease. The eGFR helps determine prognosis and treatment, such as when hemodialysis or a transplant may be needed.

Since 1999, race has been a variable used in estimating GFR. Current eGFR calculations also use a person's age, sex, and serum creatinine levels. Serum creatinine, which the kidneys filter out, is a waste product from the normal metabolism of muscle cells in one's body. Studies have shown that Black Americans, on average, can have higher levels of serum creatinine in their blood, independent of kidney function. To account for this difference, eGFR calculations include a person's self-reported race to give more valid results.

"Using race as a testing factor risks kidney disease misdiagnosis. There is great variance within the genetic ancestry of people who identify as 'Black' which means we cannot reliably view 'Black' people as being from a single ancestral group," said Afshin Parsa, MD, NIDDK program director for CRIC. "Misdiagnosis could lead to a person receiving incorrect drug dosing, or delays in receiving dialysis or a kidney transplant. Current eGFR calculations could be exacerbating racial inequities in a disease that disproportionately affects Black people, so this study set out to identify factors that wouldn't rely on including a person's race to calculate eGFR."

CRIC researchers found that even when adjusting for a wide range of factors, using serum creatinine to calculate eGFR without using a race term can lead to systematic bias and race-related misclassification of kidney disease status in people tested.

Yet, unlike serum creatinine, most biomarkers — substances that can help identify disease or stages of a disorder — aren't affected by race or ancestry. By analyzing data from CRIC participants, the researchers found that using cystatin C — which is not affected by race or ancestry — as a race-independent replacement biomarker for serum creatinine provided accurate and non-biased results.

"We hope this study's results will build momentum toward widespread adoption of cystatin C for the purposes of estimating GFR. The alternative eGFR test requires no special equipment, can be standardized, and the more it's adopted, the less it would cost," said Chi-yuan Hsu, MD, professor and chief of nephrology at University of California, San Francisco, and lead author of the study.

Photo courtesy of NIH

CRIC is one of the largest and longest-running studies looking at the causes, frequency, and consequences of chronic kidney disease, or CKD, in the United States. Nearly all CRIC's participants are people with mild to severe loss of kidney function. Since Black people are at higher risk for CKD than other groups, approximately half of CRIC participants are Black. This analysis used more than 1,200 CRIC participants' data, including measures of body mass and muscle mass, genetic ancestry data, and self-identified race.

"An accurate eGFR formula that does not rely on self-reported race is a huge leap forward for all people with, and at risk for, chronic kidney disease," said NIDDK Director Griffin P. Rodgers, MD. "NIDDK is committed to addressing health disparities, and we hope this study's finding leads to positive changes in how CKD is identified and treated—helping address the risk of systemic bias and error in diagnosing and treating a disease that already disproportionately affects Black people."

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Consuming a Diet with More Fish Fats, Less Vegetable Oils Can Reduce Migraine Headaches

NIH-funded study finds frequency, intensity of monthly migraines declined among those on higher fish oil diet.

A diet higher in fatty fish helped frequent migraine sufferers reduce their monthly number of headaches and intensity of pain compared to participants on a diet higher in vegetable-based fats and oils, according to a new study. The findings by a team of researchers from the National Institute on Aging (NIA) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA), parts of the National Institutes of Health; and the University of North Carolina (UNC) at Chapel Hill, were published in the July 3 issue of The BMJ.

This study of 182 adults with frequent migraines expanded on the team's previous work on the impact of linoleic acid and chronic pain. Linoleic acid is a polyunsaturated fatty acid commonly derived in the American diet from corn, soybean, and other similar oils, as well as some nuts and seeds. The team's previous smaller studies explored if linoleic acid inflamed migraine-related pain processing tissues and pathways in the trigeminal nerve, the largest and most complex of the body's 12 cranial nerves. They found that a diet lower in linoleic acid and higher in levels of omega-3 fatty acids (like those found in fish and shellfish) could soothe this pain pathway inflammation.

In a 16-week dietary intervention, participants were randomly assigned to one of three healthy diet plans. Participants all received meal kits that included fish, vegetables, hummus, salads, and breakfast items. One group received meals that had high levels of fatty fish or oils from fatty fish and lowered linoleic acid. A second group received meals that had high levels of fatty fish and higher linoleic acid. The third group received meals with high linoleic acid and lower levels of fatty fish to mimic average U.S. intakes.

During the intervention period, participants monitored their number of migraine days, duration, and intensity, along with how their headaches affected their abilities to function at work, school, and in their social lives, and how often they needed to take pain medications. When the study began, participants averaged more than 16 headache days per month, over five hours of migraine pain per headache day, and had baseline scores showing a severe impact on quality of life despite using multiple headache medications.

The diet lower in vegetable oil and higher in fatty fish produced between 30% and 40% reductions in total headache hours per day, severe headache hours per day, and overall headache days per month compared to the control group. Blood samples from this group of participants also had lower levels of pain-related lipids. Despite the reduction in headache frequency and pain, these same participants reported only minor improvements in migraine-related overall quality of life compared to other groups in the study.

Migraine, a neurological disease, ranks among the most common causes of chronic pain, lost work time, and lowered quality of life. More than 4 million people worldwide have chronic migraine (at least 15 migraine days per month) and over 90% of sufferers are unable to work or function normally during an attack, which can last anywhere from four hours to three days. Women between the ages of 18 and 44 are especially prone to migraines, and an estimated 18% of all American women are affected. Current medications for migraine usually offer only partial relief and can have negative side effects including sedation, and the possibility of dependence or addiction.

"This research found intriguing evidence that dietary changes have potential for improving a very debilitating chronic pain condition like migraine without the related downsides of often prescribed medications," said Luigi Ferrucci, MD, PhD, scientific director of NIA.

The NIH team was led by Chris Ramsden, a clinical investigator in the NIA and NIAAA intramural research programs, and UNC adjunct faculty member. Ramsden and his team specialize in the study of lipids — fatty acid compounds found in many natural oils — and their role in aging, especially chronic pain and neurodegenerative conditions. The UNC team was led by Doug Mann, MD, of the Department of Neurology, and Kim Faurot, PhD, of the Program on Integrative Medicine. Meal plans were designed by Beth MacIntosh, MPH, of UNC Healthcare's Department of Nutrition and Food Services.

The researchers noted that these findings serve as validation that diet-based interventions increasing omega-3 fats while reducing linoleic acid sources show better promise for helping people with migraines reduce the number and impact of headache days than fish-oil based supplements, while reducing the need for pain medications. They hope to continue to expand this work to study effects of diet on other chronic pain conditions.

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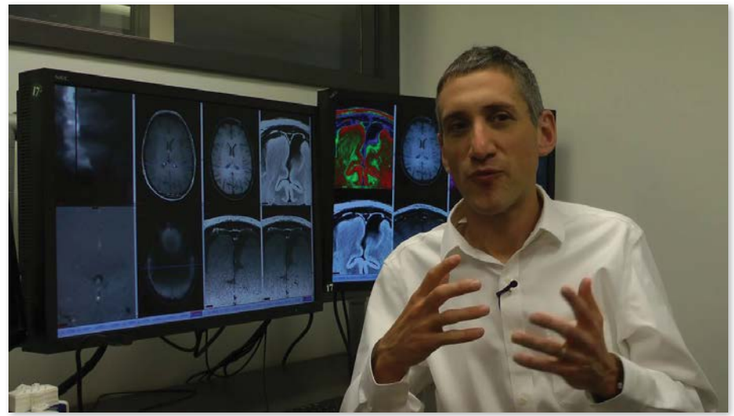
NIH Scientists Build a Cellular Blueprint of Multiple Sclerosis Lesions

Study lays the groundwork for potential new therapies for progressive multiple sclerosis

Chronic lesions with inflamed rims, or "smoldering" plaques, in the brains of people with multiple sclerosis (MS) have been linked to more aggressive and disabling forms of the disease. Using brain tissue from humans, researchers at the National Institutes of Health's National Institute of Neurological Disorders and Stroke (NINDS) built a detailed cellular map of chronic MS lesions, identifying genes that play a critical role in lesion repair and revealing potential new therapeutic targets for progressive MS. The study was published in Nature.



Senior Investigator Daniel S. Reich, MD, PhD, Translational Neuroradiology Section. Photo courtesy of NINDS

"We identified a set of cells that appear to be driving some of the chronic inflammation seen in progressive MS," said Daniel Reich, MD, PhD, senior investigator at NINDS. "These results give us a way to test new therapies that might speed up the brain's healing process and prevent brain damage that occurs over time."

Chronic active lesions are characterized by a slow, expanding rim of immune cells called microglia. Microglia normally help protect the brain, but in MS and other neurodegenerative diseases, they can become overactive and secrete toxic molecules that damage nerve cells. Other cells found at the edge of the lesions, such as astrocytes and lymphocytes, may also contribute to ongoing tissue damage. Prior studies suggest that microglia are the main culprits behind lesion expansion, but the exact types of cells found near lesions and their biological mechanisms are elusive.

To better understand MS lesions, Dr. Reich and his colleagues used single-cell RNA sequencing, a powerful technique which enables researchers to catalog gene activity patterns in individual cells, to examine post-mortem brain tissue of five MS patients and three healthy controls. Samples were provided by the Netherlands Brain Bank, Netherlands Institute for Neuroscience, Amsterdam, the Netherlands, and the NINDS Neuroimmunology Clinic.

"Single-cell RNA sequencing technology allows us to do a much deeper dive into the types of cells present in MS lesions," said Dr. Reich.

By analyzing the gene activity profiles of over 66,000 cells from human brain tissue, researchers created the first comprehensive map of cell types involved in chronic lesions, as well as their gene expression patterns and interactions.

Dr. Reich's team found a great diversity of cell types in the tissue surrounding chronic active lesions compared to normal tissue, and a high proportion of immune cells and astrocytes at the active edges of those lesions. Microglia comprised 25% of all immune cells present at the lesion edges.

"Our dataset is very rich. The beauty of having such a detailed map is that now we have a better understanding of the entire network of cells involved in smoldering inflammation," said Martina Absinta, MD, PhD, a former post-doctoral fellow in Dr. Reich's lab and current adjunct assistant professor at Johns Hopkins University, Baltimore, who led the study.

More detailed analyses revealed that the gene for complement component 1q (C1q), an important and evolutionarily ancient protein of the immune system, was expressed mainly by a subgroup of

microglia responsible for driving inflammation, suggesting that it may contribute to lesion progression.

To determine the function of C1q, researchers knocked out the gene in the microglia of mouse models of MS and examined the brain tissue for signs of neuroinflammation. In mice lacking microglial C1q, they found significantly decreased tissue inflammation compared to control animals. Additionally, in another group of animals, blocking C1q reduced iron-containing microglia, revealing a potential new therapeutic avenue to treat chronic brain inflammation in MS and related neurodegenerative diseases.

According to the authors, it's possible that targeting C1q in human microglia could halt MS lesions in their tracks.

In MS, the immune system attacks myelin, a protective layer that forms around nerve cells in the brain and spinal cord, leading to vision loss, muscle weakness, problems with balance and coordination, fatigue, numbness, and other debilitating symptoms.

Mapping multiple sclerosis lesions. Researchers used single-cell RNA sequencing to map the cells found at the edges of chronic MS lesions. Photo credit Reich lab, NIH/NINDS

A subset of people develop progressive MS, resulting in extensive brain tissue damage and disability. Anti-inflammatory medications help patients manage their symptoms by dampening the responses of immune cells in the blood and lymph nodes. But treatments are not as effective for patients with chronic lesions who experience ongoing brain tissue inflammation.

"We have terrific therapies that block new inflammation but nothing to stop the inflammation that's already there," said Dr. Reich. "In order to make strides in developing new therapies for progressive MS, we're going to need to pick apart the cellular and molecular mechanisms one by one."

In 2019, Dr. Reich and his team reported that damaging, chronic active lesions may be a hallmark of progressive MS. The current study identifies microglia and C1q as promising targets for progressive MS and supports the use of chronically inflamed rim lesions as an MRI biomarker for disease progression.

There is no cure for MS, and no therapies that directly treat chronic active lesions. By gaining a deeper understanding of lesion features, this study may help pave the way toward early clinical trials to test new therapies for this aspect of the disease.

This study was supported in part by the Intramural Research Program at the NINDS.

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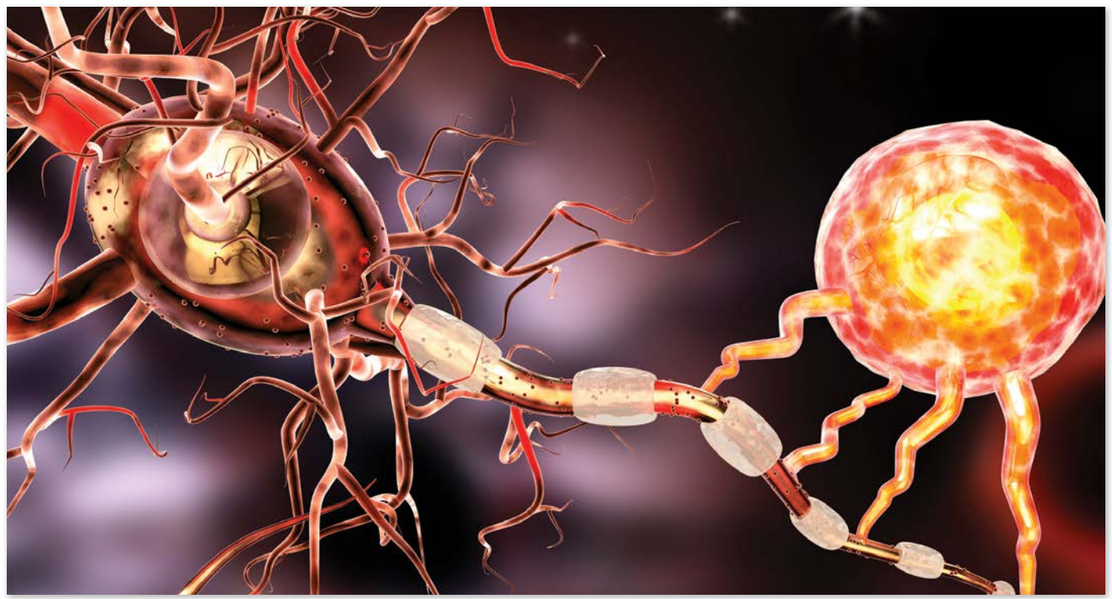


Image courtesy of NIH

Researchers Identify a Cellular Defect Common to Familial and Sporadic Forms of ALS

NIH-funded study may point to possible therapeutic target for the disease

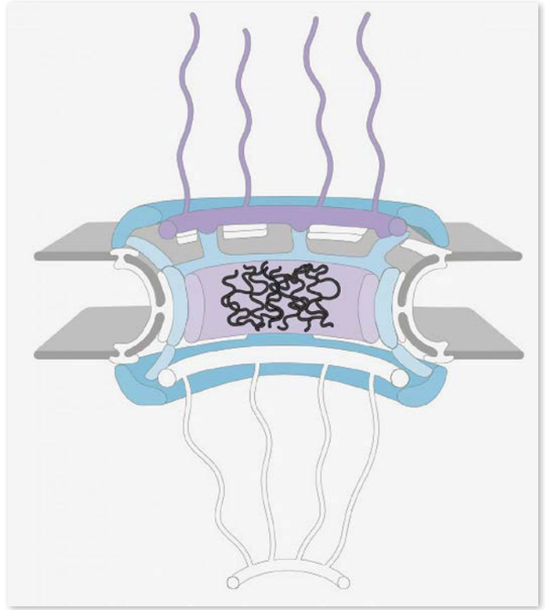
Amyotrophic lateral sclerosis (ALS) is a rapidly progressive and fatal degenerative disease affecting the nerve cells in the brain and spinal cord responsible for controlling voluntary muscle movement. "Sporadic" or non-inherited ALS, accounts for roughly 90% percent of cases, and 10% of cases are due to known genetic mutations. By studying lab-grown neurons derived from skin or blood cells from 10 normal controls, eight with an ALS causing mutation, and 17 with non-inherited ALS, researchers have found a possible starting point for the dysfunction that causes the disease. The study, which was published in Science Translational Medicine was funded in part by the National Institute for Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health.

Using a library of ALS patient-derived cells, the research team led by Jeffrey Rothstein, MD, PhD, at Johns Hopkins University School of Medicine, Baltimore, developed induced pluripotent stem cell (iPSC)-derived neurons from the patients' cultured cells to discover a common defect regardless of whether the cell came from persons with inherited or non-inherited ALS. They report that in ALS nerve cells, there is an accumulation of a protein called CHMP7 in the nucleus of cultured nerve cells as well as in ALS samples from the brain region that controls movement. Treatments that decrease the amount of CHMP7 in the cultured cells prevented a series of abnormalities that are characteristic of ALS.

"There is considerable interest in identifying new therapeutic targets for ALS, particularly for the sporadic form of the disorder," said Amelie Gubitz, PhD, program director, NINDS. "Gene-targeting strategies like the one shown here now allow us to move from biological discovery straight to therapy development."

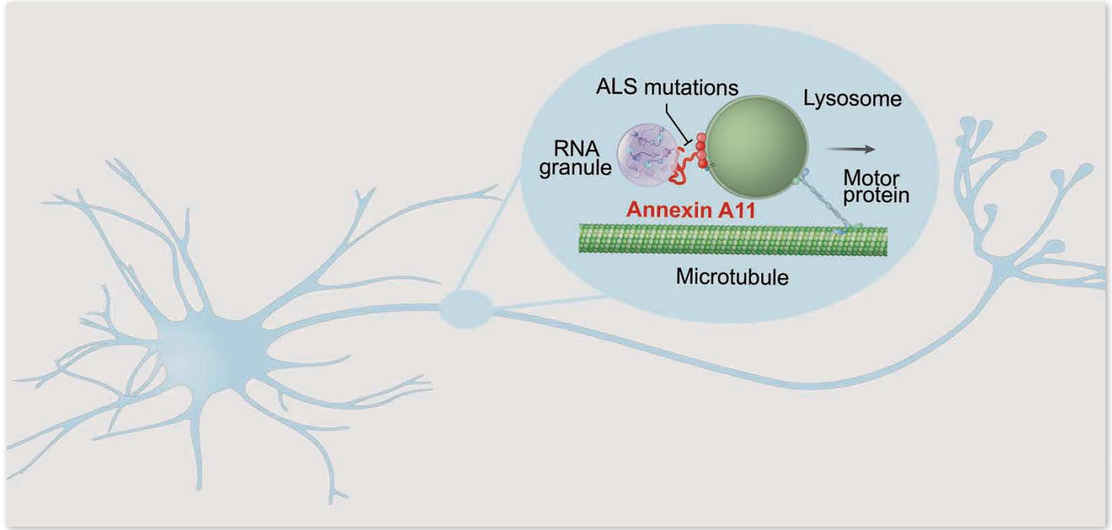
This study builds on an earlier paper by the Rothstein lab that looked at the most common genetic cause of ALS, a mutation in the C9orf72 gene (also referred to as the "C9 mutation"). There, they showed that the C9 mutation produced defects in a structure called the nuclear pore that is responsible for moving proteins and other molecules in and out of the nucleus of cells. Specifically, they found that certain proteins were absent from the pore, causing a domino-like effect in which the entire pore breaks apart.

"We knew from our previous work that the C9 mutation was producing defects in the nuclear pore, but we didn't know why," said Dr. Rothstein. "Here, we set out to answer the question of what was happening upstream of the pore defects by studying neurons derived from the cells of patients with ALS."



When CHMP7 accumulates in the nucleus, certain proteins become missing from nuclear pores (outlined in white). This causes the pores to break apart, leading to downstream effects that may cause ALS. Photo credit Rothstein Lab

Specifically, the researchers looked at nerve cells grown from induced pluripotent stem cells (iPSCs), which are a type of stem cell that can be created from samples of a person's skin or blood. These cells behave very much like other stem cells in that they can be turned into many different cell types in a lab setting, including nerve cells. By working with Answer ALS, a national ALS biological data and iPSC effort run by Rothstein, the researchers were able to access iPSCs derived from both familial and sporadic ALS patients.



Researchers discovered that annexin A11, a gene linked to a rare form of ALS, may play a critical role in the transport of RNA-encoded housekeeping instructions throughout neurons by hitching RNA granules onto traveling lysosomes and that disease-causing mutations prevent hitchhiking. Graphic courtesy of NINDS

"One of the great advantages of iPSCs is that you can look at different times very much in the same way as you would study animal models at different ages," said Dr. Rothstein. "We knew the time point where the nuclear pores began to degrade, and we were able to study neurons at earlier times to see what the cause could be."

What they found was that the accumulation of CHMP7 within the nucleus occurred at least one week prior to the development of nuclear pore abnormalities. Normally, CHMP7 is quickly removed once it enters the nucleus, but in both C9 and sporadic ALS iPSC-derived neurons, the accumulation persisted. If an antisense oligonucleotide drug, which stops cells from manufacturing specific proteins, was used to decrease the amount of CHMP7 within the ALS neurons, the pore never degraded. Finally, if a mutated form of CHMP7 that cannot be removed from the nucleus was added to healthy neurons, the pore degraded much like what was seen in ALS neurons, suggesting that the presence of CHMP7 within the nuclei of neurons could be a lynchpin event in the development of the disease.

One abnormality common to all forms of ALS is the mislocalization of another protein, TDP-43. Normally found in the nucleus, TDP-43 leaks out into the surrounding cytoplasm in ALS where it clumps together into aggregates, leading to loss of function changes in various types of RNA, which are critical for the translation of certain genes into proteins. Eventually this is also seen in iPSC-derived neurons from both C9 and sporadic ALS patients. Following treatment with the antisense oligonucleotides for CHMP7, the TDP-43 mislocalization was no longer seen and the RNA defects were all corrected.

"These findings together allow us to put these abnormalities in sequence, where CHMP7 accumulation in the nucleus leads to nuclear pore injury, followed by TDP-43 mislocalization, and ultimately cell death," said Dr. Rothstein. "This is not just limited to the C9 mutation; it is a fundamental pathway in sporadic ALS as well that can be treated with antisense oligonucleotides for CHMP7."

Dr. Rothstein's lab is currently investigating whether the antisense oligonucleotide drug could be developed into a treatment for both C9 and sporadic ALS patients. They are also continuing to study the initial accumulation of CHMP7 to determine what causes the mislocalization in the nucleus.

This study was supported by grants from the NIH (NS099114, NS091046, NS094239, NS122236), the U.S. Department of Defense, The Robert Packard Center for ALS Research Answer ALS Program, ALS Association, Muscular Dystrophy Association, Virginia Gentleman Foundation, F Prime, the Chan Zuckerberg Initiative, and an ALSA Milton Safenowitz Postdoctoral Fellowship.

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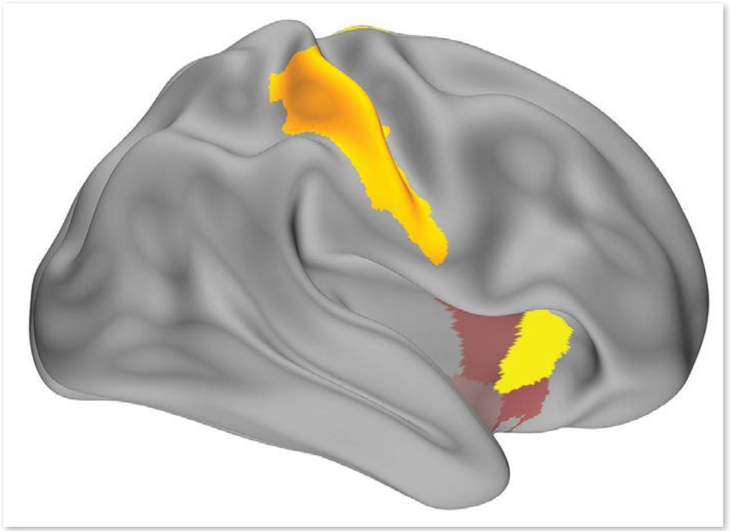
Study Shows How Taking Short Breaks May Help Our Brains Learn New Skills

NIH scientists discover that the resting brain repeatedly replays compressed memories of what was just practiced.

In a study of healthy volunteers, National Institutes of Health researchers have mapped out the brain activity that flows when we learn a new skill, such as playing a new song on the piano, and discovered why taking short breaks from practice is a key to learning. The researchers found that during rest the volunteers' brains rapidly and repeatedly replayed faster versions of the activity seen while they practiced typing a code. The more a volunteer replayed the activity the better they performed during subsequent practice sessions, suggesting rest strengthened memories.



In a study of healthy volunteers, NIH researchers discovered that our brains may replay compressed memories of learning new skills when we rest. Above is a map of the memory replay activity observed in the study. Photo credit Cohen lab, NINDS

"Our results support the idea that wakeful rest plays just as important a role as practice in learning a new skill. It appears to be the period when our brains compress and consolidate memories of what we just practiced," said Leonardo G. Cohen, MD, senior investigator at the NIH's National Institute of Neurological Disorders and Stroke (NINDS) and the senior author of the study published in Cell Reports. "Understanding this role of neural replay may not only help shape how we learn new skills but also how we help patients recover skills lost after neurological injury like stroke."

The study was conducted at the NIH Clinical Center. Dr. Cohen's team used a highly sensitive scanning technique, called magnetoencephalography, to record the brain waves of 33 healthy, right-handed volunteers as they learned to type a five-digit test code with their left hands. The subjects sat in a chair and under the scanner's long, cone-shaped cap. An experiment began when a subject was shown the code "41234" on a screen and asked to type it out as many times as possible for 10 seconds and then take a 10 second break. Subjects were asked to repeat this cycle of alternating practice and rest sessions a total of 35 times.

During the first few trials, the speed at which subjects correctly typed the code improved dramatically and then leveled off around the 11th cycle. In a previous study, led by former NIH postdoctoral fellow Marlene Bönstrup, MD, Dr. Cohen's team showed that most of these gains happened during short rests, and not when the subjects were typing. Moreover, the gains were greater than those made after a night's sleep and were correlated with a decrease in the size of brain waves, called beta rhythms. In this new report, the researchers searched for something different in the subjects' brain waves.

"We wanted to explore the mechanisms behind memory strengthening seen during wakeful rest. Several forms of memory appear to rely on the replaying of neural activity, so we decided to test this idea out for procedural skill learning," said Ethan R. Buch, PhD, a staff scientist on Dr. Cohen's team and leader of the study.

To do this, Leonardo Claudino, PhD, a former postdoctoral fellow in Dr. Cohen's lab, helped Dr. Buch develop a computer program which allowed the

Photo courtesy of NIH

team to decipher the brain wave activity associated with typing each number in the test code.

The program helped them discover that a much faster version — about 20 times faster — of the brain activity seen during typing was replayed during the rest periods. Over the course of the first eleven practice trials, these compressed versions of the activity were replayed many times — about 25 times — per rest period. This was two to three times more often than the activity seen during later rest periods or after the experiments had ended.

Interestingly, they found that the frequency of replay during rest predicted memory strengthening. In other words, the subjects whose brains replayed the typing activity more often showed greater jumps in performance after each trial than those who replayed it less often.

"During the early part of the learning curve we saw that wakeful rest replay was compressed in time, frequent, and a good predictor of variability in learning a new skill across individuals," said Dr. Buch. "This suggests that during wakeful rest the brain binds together the memories required to learn a new skill."

As expected, the team discovered that the replay activity often happened in the sensorimotor regions of the brain, which are responsible for controlling movements. However, they also saw activity in other brain regions, namely the hippocampus and entorhinal cortex.

"We were a bit surprised by these last results. Traditionally, it was thought that the hippocampus and entorhinal cortex may not play such a substantive role in procedural memory. In contrast, our results suggest that these regions are rapidly chattering with the sensorimotor cortex when learning these types of skills," said Dr. Cohen. "Overall, our results support the idea that manipulating replay activity during waking rest may be a powerful tool that researchers can use to help individuals learn new skills faster and possibly facilitate rehabilitation from stroke."

This study was supported by the NIH Intramural Research Program at the NINDS.

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NIH Invests in Next Iteration of Public-private Partnership to Advance Precision Medicine Research for Alzheimer's Disease

Part of the Accelerating Medicines Partnership to develop effective targeted therapies

By the NIH Office of Communications and Public Liaison, NIH News Media Branch

The National Institutes of Health has launched the next version of the Accelerating Medicines Partnership (AMP) Alzheimer's disease program (AMP AD 2.0) to expand the open science, big data approach for identifying biological targets for therapeutic intervention. AMP AD 2.0 is supporting new technologies, including cutting-edge, single-cell profiling, and computational modeling, to enable a precision medicine approach to therapy development. Managed through the Foundation for the NIH (FNIH), AMP AD 2.0 brings together NIH, industry, nonprofit and other organizations with a shared goal of using open science practices to accelerate the discovery of new drug targets, biomarkers, and disease subtypes.

Richard J. Hodes, MD, Director, National Institute on Aging, National Institutes of Health. Photo courtesy of NIA

"Unraveling the complex biological mechanisms that cause Alzheimer's disease is critical for therapeutic development," said NIH Director Francis S. Collins, MD, PhD. "AMP AD 2.0 aims to add greater precision to the molecular maps developed in the first iteration of this program. This will identify biological targets and biomarkers to inform new therapeutic interventions for specific disease subtypes."

Alzheimer's, the most common cause of dementia, affects an estimated 5.8 million Americans 65 and older. Because the prevalence of this disease is greater among Black and Latino Americans than among white Americans, AMP AD 2.0 will expand the molecular characterization of Alzheimer's in brain, blood, and spinal fluid samples collected in these diverse populations. These datasets will allow the AMP AD 2.0 research teams to refine the characterization of new targets, discover new fluid biomarkers, define disease subtypes, and increase the understanding of causative factors and steps in disease progression. The knowledge gained will inform the development of therapies that can be tailored to different stages of the disease and diverse disease risk profiles.

"AMP AD has helped transform the way we learn about the disease process and identify new targets for treatment," said Richard J. Hodes, MD, director of the National Institute on Aging (NIA), part of NIH. "By expanding the molecular characterization of Alzheimer's disease to be more inclusive of diverse populations and by renewing the commitment to open science practices for sharing data, methods, and results, we will enable researchers across the globe to better understand the complex nature of the disease and take a precision medicine approach to the development of effective treatments."

During the first AMP Alzheimer's program, research teams generated a wealth of high-quality data from human biological samples and animal and cell-based models and discovered more than 500 unique candidate targets through unbiased computational methods. These novel data resources were made available through a centralized data infrastructure and data-sharing platform, the AD Knowledge Portal, and the portal-linked, open-source platform Agora. The wide availability of this data has led to many new insights on the role of the genome, proteome, metabolome, and microbiome in the disease process. To date, more than 3,000 researchers around the world, representing academic, biotechnology, and pharmaceutical industry sectors, have used these data resources for research on Alzheimer's and related dementias.

NIA will lead research efforts and contribute an estimated total of $61.4 million over five years, pending availability of funds. This includes funding for a data coordinating center at Sage Bionetworks, and six multi-institutional, cross-disciplinary academic research teams.

AMP AD 2.0 private funding partners include Eisai Inc., Gates Ventures, and Takeda Pharmaceutical Company Limited. The Alzheimer's Association and GlaxoSmithKline plc (GSK), who have been partners since the beginning of the AMP Alzheimer's program, will again participate and continue to provide support towards the program's goals. The total co-funding contribution from all private partners will be approximately $13.45 million, which will be managed through FNIH.

As before, FNIH will manage a steering committee to provide strategic direction of the partnership's research plans with representation from public- and private-sector partners. FNIH's steering committee management will be directed by an AMP AD executive committee made up of leaders from NIA, industry,

the U.S. Food and Drug Administration, and not-for-profit research, advocacy, and care organizations.

"This partnership offers real hope to the tens of millions of people affected by Alzheimer's disease," said Maria C. Freire, PhD, president and executive director of the FNIH. "Collaboration through the first round of AMP AD has already enabled breakthrough advances in researchers' understanding of how Alzheimer's disease progresses, uncovering numerous potential targets for drug therapy in a field where treatment options are severely limited."

nia.nih.gov

U.S. Burden of Alzheimer's Disease, Related Dementias to Double by 2060

CDC study first to forecast Alzheimer's estimates by race/ethnicity

The U.S. burden of Alzheimer's disease and related dementias (ADRD) will double by 2060, according to a new study from the Centers for Disease Control and Prevention.

The study, published online in Alzheimer's & Dementia: The Journal of the Alzheimer's Association, is the first to forecast Alzheimer's disease by race and ethnicity. CDC researchers predict that Hispanic Americans will have the largest projected increase due to population growth over the projection period, although because of the relative size of the population, non-Hispanic whites will still have the largest total number of Alzheimer's cases.

The burden of Alzheimer's disease and related dementias in 2014 was 5 million people, which is 1.6 percent of the U.S. population in 2014 — 319 million people. This burden is projected to grow to 13.9 million, nearly 3.3 percent of the population in 2060 — 417 million people.

"This study shows that as the U.S. population increases, the number of people affected by Alzheimer's disease and related dementias will rise, especially among minority populations," said CDC Director Robert R. Redfield, MD. "Early diagnosis is key to helping people and their families cope with loss of memory, navigate the health care system, and plan for their care in the future."

Racial disparities in future burden of Alzheimer's

Alzheimer's disease is the fifth most common cause of death for Americans ages 65 years and older. It is an irreversible, progressive brain disorder that slowly destroys memory and, eventually, a person's ability to perform even the simplest tasks, such as bathing, feeding, and dressing.

CDC researchers estimated the number of people with Alzheimer's by age, sex, race and ethnicity in 2014 and 2060 based on population projections from the U.S. Census Bureau and percentages of Medicare Fee-for-Service beneficiaries ages 65 years and older with Alzheimer's disease and related dementias from the Centers for Medicare & Medicaid Services.

Key findings

Among people ages 65 and older, African Americans have the highest prevalence of Alzheimer's disease and related dementias (13.8 percent), followed by Hispanics (12.2 percent), and non-Hispanic whites (10.3 percent), American Indian and Alaska Natives (9.1 percent), and Asian and Pacific Islanders (8.4 percent).

By 2060, the researchers estimate there will be 3.2 million Hispanics and 2.2 million African Americans with Alzheimer's disease and related dementias. The increases are a result of fewer people dying from other chronic diseases and surviving into older adulthood when the risk for Alzheimer's disease and related dementias increases.

Caregivers of people living with Alzheimer's and related dementias need support

The report also addresses the need to provide support to caregivers of persons living with Alzheimer's and related dementias because an early diagnosis can help caregivers plan for the life-changing experience of caring for a friend or family member with these conditions, which can also impact the caregiver's health and well-being.

"It is important for people who think their daily lives are impacted by memory loss to discuss these concerns with a health care provider. An early assessment and diagnosis is key to planning for their health care needs, including long-term services and supports, as the disease progresses," said Kevin Matthews, PhD, health geographer and lead author of the study with the CDC's Division of Population Health within the National Center for Chronic Disease Prevention and Health Promotion.

CDC works to understand and improve the lives of people with Alzheimer's and related dementias, and their families, by:

- Collecting, analyzing, and disseminating data on cognitive decline and caregiving to guide public health action.
- Promoting awareness of Alzheimer's disease and other dementias, including the importance of early assessment and diagnosis.
- Collaborating with partners to develop, promote, and disseminate effective strategies to train health care workers about early signs of dementia despite cultural differences.

NIH Expands Alzheimer's and Related Dementias Centers Research Network

New North Carolina and Texas centers to enhance collaborative studies with diverse populations

By Joe Balintfy

Research institutions in North Carolina and Texas are the latest to join an established, nationwide network of cutting-edge Alzheimer's disease and related dementias centers funded by the National Institute on Aging (NIA), part of the National Institutes of Health (NIH). The Duke/University of North Carolina Alzheimer's Disease Research Center and the South Texas Alzheimer's Disease Center have each been awarded $14.8 million over five years to bolster a range of research areas, including early and midlife risk factors for Alzheimer's and related dementias, and ways to understand and diminish the burden of these diseases on understudied groups, specifically Mexican-American Hispanics and Black/African Americans, which are among the fastest-growing older populations in the United States.

"NIA-funded Alzheimer's Disease Research Centers (ADRC) have been at the heart of progress in Alzheimer's and related dementias research in the U.S. for more than three decades," said NIA Director Richard J. Hodes, MD. "Funding these two new research hubs underscores our ongoing commitment to finding effective preventions and treatments for a diverse range of individuals at risk for and living with these diseases."

Enhanced national connections for communities and researchers
With these two new entities, there are now 33 ADRCs nationwide, plus four exploratory centers, that are accelerating research on effective Alzheimer's and related dementias preventions, diagnostics, and treatments, and improving support for families and other caregivers.

"Alzheimer's Disease Research Centers bring together scientists and research participants with a wide range of research focus areas, within each center and across the network," said Nina Silverberg, PhD, director of NIA's ADRC program. "These two new centers will be important contributors as we continue to build momentum toward new research approaches to treatment and prevention as well as caregiving strategies, and importantly, toward inclusion of a diverse group of research volunteers reflective of those most affected by the disease."

The new Duke/UNC ADRC represents a collaboration of leading researchers in aging and Alzheimer's and related dementias at Duke University and the University of North Carolina at Chapel Hill. This center will focus on identifying age-related changes across the lifespan that impact the development, progression, and experience of Alzheimer's and related dementias. The center will also identify how factors that arise in early and midlife contribute to racial, ethnic and geographic disparities in dementia.

The University of Texas Health Science Center at San Antonio and The University of Texas Rio Grande Valley ADRC will harness its unique geographic location in South Texas — a region of approximately 5 million underserved Mexican Americans — to build connections with the community and enhance the diversity of data and biosamples available through the national network of ADRCs. These efforts will support researchers from multiple disciplines to conduct research to reduce the burden of Alzheimer's and related dementias in Hispanics and will rapidly advance the science by sharing these resources broadly.

ADRCs are a backbone for Alzheimer's and related dementias research

Since NIA established the network in 1984, ADRC scientists have helped advance research on many aspects of Alzheimer's and related dementias, including:

- Developing a better understanding of amyloid plaque and tau tangle formation, which are two hallmarks of Alzheimer's.
- Characterizing abnormal proteins linked to multiple neurodegenerative diseases.
- Distinguishing between cognitive changes that occur in normal aging from those that indicate a transition to dementia.
- Exploring changes in the brain and body through the clinical stages of Alzheimer's and related dementias.
- Developing novel biomarkers for the early detection of Alzheimer's and related disorders.
- Working with diverse populations aiming to ensure clinical studies include participants from a range of ages, races, and ethnicities.
- Supporting vitally important brain donation programs that enable researchers to better understand how Alzheimer's and related dementias affect the brain.
- Sharing a large set of standardized data on thousands of research volunteers, made available to scientists around the world, to use to help better understand Alzheimer's and other dementias and look for treatments.
- Conducting clinical studies to discover new targets and potential treatments of Alzheimer's and related disorders.

nia.nih.gov

In a Common Genetic Disorder, Blood Test Reveals when Benign Tumors Turn Cancerous

People with an inherited condition known as neurofibromatosis type 1, or NF1, often develop non-cancerous, or benign, tumors that grow along nerves. These tumors can sometimes turn into aggressive cancers, but there hasn't been a good way to determine whether this transformation to cancer has happened.

Researchers from the National Cancer Institute's (NCI) Center for Cancer Research, part of the National Institutes of Health, and Washington University School of Medicine in St. Louis have developed a blood test that, they believe, could one day offer a highly sensitive and inexpensive approach to detect cancer early in people with NF1. The blood test could also help doctors monitor how well patients are responding to treatment for their cancer.

The findings are published in the August 31 issue of *PLOS Medicine*.

NF1 is the most common cancer predisposition syndrome, affecting 1 in 3,000 people worldwide. The condition, caused by a mutation in a gene called NF1, is almost always diagnosed in childhood. Roughly half of people with NF1 will develop large but benign tumors on nerves, called plexiform neurofibromas.

In up to 15% of people with plexiform neurofibromas, these benign tumors turn into an aggressive form of cancer known as malignant peripheral nerve sheath tumor, or MPNST. Patients with MPNST have a poor prognosis because the cancer can quickly spread and often becomes resistant to both chemotherapy and radiation. Among people diagnosed with MPNST, 80% die within five years.

Doctors may soon be able to use a blood test to distinguish between benign and cancerous tumors in people with NF1. Photo credit NIH and iStock

"Imagine going through life with a cancer predisposition syndrome like NF1. It's kind of like a ticking bomb," said study co-author Jack F. Shern, MD, a Lasker Clinical Research Scholar in NCI's Pediatric Oncology Branch. "The doctors are going to be watching for cancerous tumors, and you're going to be watching for them, but you really want to discover that transformation to cancer as early as possible."

Doctors currently use either imaging scans (MRI or PET scan) or biopsies to determine if plexiform neurofibromas have transformed into MPNST. However, biopsy findings aren't always accurate and the procedure can be extremely painful for patients because the tumors grow along nerves. Imaging tests, meanwhile, are expensive and can also be inaccurate.

"What we don't have right now is a tool to help us determine if within that big, bulky benign plexiform neurofibroma, something bad is cooking and it's turning into an MPNST," Dr. Shern said. "So we thought, 'What if we developed a simple blood test where instead of a full-body MRI or a fancy PET scan, we could just draw a tube of blood and say whether or not the patient has an MPNST somewhere?'"

In pursuit of this goal, Dr. Shern and study co-leads Aadel A. Chaudhuri, MD, PhD, and Angela C. Hirbe, MD, PhD, of Washington University School of Medicine, and their collaborators collected blood samples from 23 people with plexiform neurofibromas, 14 patients with MPNST that had not yet been treated, and 16 healthy people without NF1. Most of the study participants were adolescents and young adults, the age group in which MPNST most often develops. The researchers isolated cell-free DNA — that is, DNA shed from cells into the blood — from the blood samples and used whole-genome sequencing technology to look for differences in the genetic material among the three groups.

The cell-free DNA in patients with MPNST had several features that distinguished it from the DNA in the other two groups. For example, patients with MPNST had pieces of cell-free DNA that were shorter than those in people with plexiform neurofibromas or without NF1. In addition, the proportion of cell-free DNA that comes from tumors — called the "plasma tumor fraction" — in the blood samples was much higher in people with MPNST than in those with plexiform neurofibromas. Together, these differences allowed the researchers to differentiate, with 86% accuracy, between patients with plexiform neurofibromas and those with MPNST.

In the study participants with MPNST, the plasma tumor fraction also aligned with how well they responded to treatment. In other words, if their plasma tumor fraction decreased following treatment, the size and number of their tumors (as measured by imaging scans) also decreased. An increase in plasma tumor fraction was associated with metastatic recurrence.

"You can imagine treating a patient with a chemotherapy regimen. This blood test could easily and rapidly allow us to determine whether the disease is going down or maybe even going away entirely," Dr. Shern said. "And if you had done surgery and taken out an MPNST, and the blood test was negative, you could use that to monitor the patient going forward to see if the tumor returns."

Dr. Shern noted that one limitation of the current study is its small size, even though it included people with NF1 from two large hospitals. The researchers are planning to conduct a larger trial with more patients. Dr. Shern said the team's goal is to increase the accuracy of the blood test from 86% to closer to 100%. One approach would be to refine the genetic analysis to focus on genes known to be involved in MPNST.

A simple and inexpensive blood test to detect MPNST early in NF1 patients would be especially useful in developing countries and other resource-poor areas, where access to the equipment and expertise needed to perform imaging is limited, Dr. Shern said.

Blood tests of this type also have applications in the early detection and monitoring of patients with other cancer-predisposing genetic disorders, such as multiple endocrine neoplasia, in which benign tumors can turn cancerous, or Li-Fraumeni syndrome, which increases one's risk for developing several types of cancer.

"This is the perfect opportunity to apply these technologies where we can use a simple blood test to screen an at-risk population," said Dr. Shern. "If the test shows something abnormal, that's when we know to act and go looking for a tumor."

The study was supported by the Intramural Research Program of NCI and the National Institute of General Medical Sciences, another part of NIH.

Reference

Szymanski JJ, Sundby RT, Jones PA, et al. Cell-free DNA ultra-low-pass whole genome sequencing to distinguish malignant peripheral nerve sheath tumor (MPNST) from its benign precursor lesion: A cross-sectional study. PLoS Med 2021;18(8). DOI: 10.1371/journal.pmed.1003734

cancer.gov

Engineered Immune Cells Deliver Anticancer Signal, Prevent Cancer from Spreading

Scientists have genetically engineered immune cells, called myeloid cells, to precisely deliver an anticancer signal to organs where cancer may spread. In a study of mice, treatment with the engineered cells shrank tumors and prevented the cancer from spreading to other parts of the body. The study, led by scientists at the National Cancer Institute's (NCI) Center for Cancer Research, part of the National Institutes of Health (NIH), was published March 24, 2021, in Cell.

"This is a novel approach to immunotherapy that appears to have promise as a potential treatment for metastatic cancer," said the study's leader, Rosandra Kaplan, MD, of NCI's Center for Cancer Research.

Metastatic cancer — cancer that has spread from its original location to other parts of the body — is notoriously difficult to treat. Dr. Kaplan's team has been exploring another approach: Preventing cancer from spreading in the first place.

Before cancer spreads, it sends out signals that get distant sites ready for the cancer's arrival — like calling ahead to have the pillows fluffed in your hotel room prior to arrival. These "primed and ready" sites, discovered by Dr. Kaplan in 2005, are called premetastatic niches.

In the new study, the NCI team explored the behavior of immune cells in the premetastatic niche. Because Dr. Kaplan is a pediatric oncologist, the team mainly studied mice implanted with rhabdomyosarcoma, a type of cancer that develops in the muscles of children and often spreads to their lungs.

To study the premetastatic niche, the researchers looked at the lungs of the mice after tumors formed in the leg muscle but before the cancer was found in the lungs. The immune system's natural ability to attack cancer was present but actively stifled in the lungs, the NCI scientists discovered. There were few cancer-killing immune cells, but many cells that suppress the immune system.

Myeloid cells, in particular, were abundant in the premetastatic niche and continued to gather there as the cancer progressed. Myeloid cells are part of the body's first response to infection, injury, and cancer. When they detect a threat, they normally make interleukin 12 (IL-12), a signal that alerts and activates other immune cells. But myeloid cells in the lung premetastatic niche instead sent out signals that told cancer-fighting immune cells to stand down, the researchers found.

Together, these features of the lung premetastatic niche allow cancer cells to thrive when they spread there, Dr. Kaplan explained.

The NCI team wondered if they could take advantage of myeloid cells to spur the immune system into action in the premetastatic niche by changing the message they deliver. So, they used genetic engineering to add an extra gene for IL-12 to myeloid cells from lab mice.

"We chose myeloid cells to deliver IL-12 based on their unique ability to home to tumors and metastatic sites," Dr. Kaplan said. "With IL-12, we're turning the volume up on a message that's been quieted."

Rosandra Kaplan, MD. Photo courtesy of cancer.gov

In mice with rhabdomyosarcoma, these genetically engineered myeloid cells, nicknamed GEMys, produced IL-12 in the primary tumor and in metastatic sites. As hoped, the GEMys recruited and activated cancer-killing immune cells in the premetastatic niche and lowered the signals that suppress the immune system, the researchers found.

"We were excited to see that the GEMys 'changed the conversation' in the premetastatic niche. They were now telling other immune cells to get ready to fight the cancer," Dr. Kaplan said.

As a result, mice treated with GEMys had less metastatic cancer in the lungs, smaller tumors in the muscle, and they lived substantially longer than mice treated with nonengineered myeloid cells. The researchers found similar results when they studied mice with pancreatic tumors that spread to the liver.

The NCI team also found that, in combination with chemotherapy, surgery, or T-cell transfer therapy, the effects of the GEMy treatment improved. For example, giving mice a single dose of chemotherapy two days before the GEMy infusion cured mice with rhabdomyosarcoma, meaning the treatment completely eliminated all traces of cancer for more than 100 days.

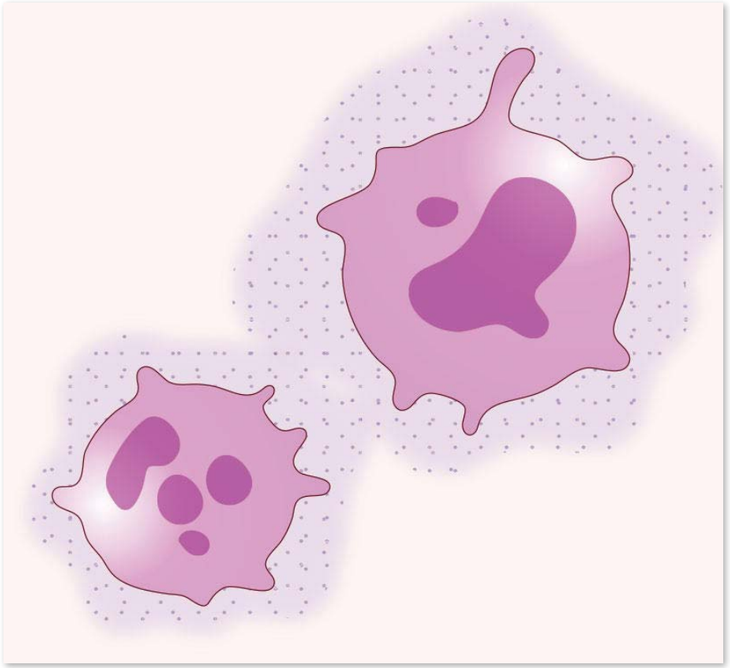
"I have never seen that kind of durable cure in my research before. Typically, cancer growth will slow down after treatment, but then it will come back with a vengeance," Dr. Kaplan said.

The team also found evidence that the chemotherapy and GEMys combination might prevent cancer from coming back. When the researchers reintroduced cancer cells into mice that had been cured by the combination treatment, tumors didn't form. This suggests that the combination treatment leaves a long-lasting "immune memory" of the cancer, the researchers explained.

As a final step in their study, the researchers created GEMys from human cells grown in the lab. In lab dishes, the genetically engineered human cells produced IL-12 and activated cancer-killing immune cells.

Before cancer spreads, it sends out signals that get distant sites ready for the cancer's arrival — like calling ahead to have the pillows fluffed in your hotel room prior to arrival.

The team plans to test the safety of human GEMys in a clinical trial of adults with cancer and, if it proves to be safe, in children and adolescents with cancer. There are many unanswered questions they hope to explore, including whether the homing pattern of GEMys is similar in humans and mice, and whether IL-12 from the GEMys will cause side effects in patients.



NCI scientists have genetically engineered myeloid cells (pink) to deliver an anticancer signal (purple dots) to sites where cancer may spread. Photo courtesy of the National Cancer Institute

But the researchers are reassured by several factors. "We are delivering a small amount of IL-12 that's similar to the body's natural response to an infection, creating a ripple effect of immune activation against the cancer. In addition, GEMys don't multiply rapidly inside the body, so they're not flooding the system with IL-12," explained Sabina Kaczanowska, PhD, first author of the study. These are important considerations because high levels of IL-12 throughout the body can be toxic.

"Although there are challenges of planning a first-in-human trial of a cell therapy, I'm grateful to have access to the resources of the NIH Clinical Center and to be able to lean on the experience of my NCI colleagues who have had decades of experience developing cell therapies for cancer," Dr. Kaplan added.

Reference

Kaczanowska S, Beury DW, Gopalan V, et al., Genetically engineered myeloid cells rebalance the core immune-suppression program in metastasis. Cell. March 24, 2021. DOI: 10.1016/j.cell.2021.02.048

cancer.gov

International Coalition Classifies 25 Subtypes of Uveitis, an Inflammatory Eye Disease

NIH-funded classification criteria will facilitate clinical research for new therapies

An international coalition of eye researchers used machine learning to develop classification criteria for 25 of the most common types of uveitis, a collection of over 30 diseases characterized by inflammation inside the eye. Together, these diseases are the fifth leading cause of blindness in the United States. The Standardization of Uveitis Nomenclature (SUN) Working Group, funded by the National Eye Institute (NEI), published its classification criteria in the American Journal of Ophthalmology. NEI is part of the National Institutes of Health.

"In the past, clinical research in the field of uveitis has been hampered by the lack of widely-accepted and validated diagnostic criteria," said Douglas A. Jabs, MD, MBA, the SUN project leader and professor of epidemiology and ophthalmology, Johns Hopkins Bloomberg School of Public Health, Baltimore. "These classification criteria are a major step forward for epidemiological studies, translational studies, pathogenesis research, outcomes research, and clinical trials. They hopefully will yield better disease-specific approaches to diagnosis and treatment."

In uveitis, inflammation can be seen in the anterior chamber (anterior uveitis), vitreous (intermediate uveitis), choroid, or retina (posterior uveitis), or all of these (panuveitis). Disease course, complications of uveitis, and the effect on vision vary dependent on the specific disease. Some uveitis appears abruptly and resolves. But many cases are recurrent or chronic, requiring long-term therapy. Symptoms may include floaters, vision loss, pain, and light sensitivity. Uveitis can strike at any age and can have a major impact on quality of life.

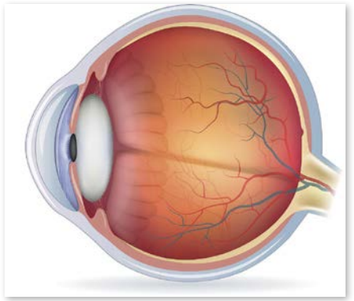


Photo courtesy of NEI

Until recently, classification of uveitis was based on the primary location of inflammation. However, types of uveitis affecting the same anatomic location can have different causes, courses, prognoses, and treatment needs. Previous work by the SUN Working Group demonstrated that even uveitis experts can disagree on diagnosis, making apples-to-apples comparisons difficult when conducting clinical research.

"The agreement among uveitis experts on the diagnosis of individual diseases was modest at best. So, we set off to try to provide clarity, using informatics, formal consensus techniques, and technology to assist in classifying each uveitic disease," said Jabs.

The SUN Working Group, a team of nearly 100 international uveitis experts from more than 20 countries and 60 clinical centers, worked together throughout the project, which was conducted in four phases: informatics, case collection, case selection, and machine learning. The researchers used machine learning, a type of artificial intelligence, to help them identify the important characteristics that distinguished each disease.

The informatics phase involved standardizing language to describe each type of uveitis and the mapping of terms to individual diseases. In the case collection phase, the team entered 5,766 cases into a database, averaging 100-250 of each uveitis type. During the case selection phase, committees of nine uveitis experts reviewed the cases and used formal consensus techniques to determine whether they were a specific identifiable disease. Only cases with a more than 75% agreement among experts were included in the final database. The resulting cases (4,046) were put through machine learning using multiple approaches on a subset of the cases ("training set") and the performance of the criteria determined on a second subset of the cases (the "validation set").

The overall performance of the criteria was over 90% within uveitic class, suggesting that the criteria can be used in clinical and translational research. The final step was approval of the proposed criteria by the SUN Working Group.

"The SUN Working Group is excited about this unprecedented effort coming to fruition and the publication of this work, as it should provide the basis for future clinical research in the field of uveitis." concluded Dr. Jabs.

The work was supported by grant R01 EY026593-05.

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Scientists Discover Gene Therapy Provides Neuroprotection to Prevent Glaucoma Vision Loss

An NIH-funded research project found that calcium modulator CaMKII protects the optic nerve in mice, opening the door to new sight-saving therapy

A form of gene therapy protects optic nerve cells and preserves vision in mouse models of glaucoma, according to research supported by NIH's National Eye Institute. The findings suggest a way forward for developing neuroprotective therapies for glaucoma, a leading cause of visual impairment and blindness. The report was published in Cell.

Glaucoma results from irreversible neurodegeneration of the optic nerve, the bundle of axons from retinal ganglion cells that transmits signals from the eye to the brain to produce vision. Available therapies slow vision loss by lowering elevated eye pressure, however some glaucoma progresses to blindness despite normal eye pressure. Neuroprotective therapies would be a leap forward, meeting the needs of patients who lack treatment options.

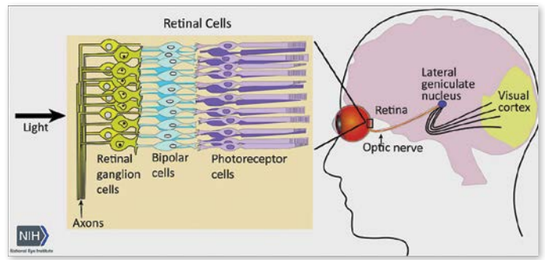
"Our study is the first to show that activating the CaMKII pathway helps protect retinal ganglion cells from a variety of injuries and in multiple glaucoma models," said the study's lead investigator, Bo Chen, PhD, associate professor of ophthalmology and neuroscience at the Icahn School of Medicine at Mount Sinai in New York City.

The CaMKII (calcium/calmodulin-dependent protein kinase II) pathway regulates key cellular processes and functions throughout the body, including retinal ganglion cells in the eye. Yet the precise role of CaMKII in retinal ganglion cell health is not well understood. Inhibition of CaMKII activity, for example, has been shown to be either protective or detrimental to retinal ganglion cells, depending on the conditions.

Using an antibody marker of CaMKII activity, Chen's team discovered that CaMKII pathway signaling was compromised whenever retinal ganglion cells were exposed to toxins or trauma from a crush injury to the optic nerve, suggesting a correlation between CaMKII activity and retinal ganglion cell survival.

Searching for ways to intervene, they found that activating the CaMKII pathway with gene therapy proved protective to the retinal ganglion cells. Administering the gene therapy to mice just prior to the toxic insult (which initiates rapid damage to the cells), and just after optic nerve crush (which causes slower damage), increased CaMKII activity and robustly protected retinal ganglion cells.

Among gene therapy-treated mice, 77% of retinal ganglion cells survived 12 months after the toxic insult compared with 8% in control mice. Six months following optic nerve crush, 77% of retinal ganglion cells had survived versus 7% in controls.



Light enters the front of the eye and reaches the retina. Photoreceptors at the back of the retina convert light into signals and sends them to bipolar and retinal ganglion cells. Axons from retinal ganglion cells form the optic nerve, which carries signals from the eye to regions of the brain that process vision. Illustration courtesy of the National Eye Institute.

Similarly, boosting CaMKII activity via gene therapy proved protective of retinal ganglion cells in glaucoma models based on elevated eye pressure or genetic deficiencies.

Increasing retinal ganglion cell survival rates translated into greater likelihood of preserved visual function, according to cell activity measured by electroretinogram and patterns of activity in the visual cortex.

Three vision-based behavioral tests also confirmed sustained visual function among the treated mice. In a visual water task, the mice were trained to swim toward a submerged platform on the basis of visual stimuli on a computer monitor. Depth perception was confirmed by a visual cliff test based on the mouse's innate tendency to step to the shallow side of a cliff. Lastly, a looming test determined that treated mice were more apt to respond defensively (by hiding, freezing or tail rattling) when shown an overhead stimulus designed to simulate a threat, compared with untreated mice.

"If we make retinal ganglion cells more resistant and tolerant to the insults that cause cell death in glaucoma, they might be able to survive longer and maintain their function," Chen concluded.

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Disarming a Blood-clotting Protein Prevents Gum Disease in Mice

Human and animal study offers insight into treating periodontal disease and other inflammatory disorders

Blocking function of a blood-clotting protein prevented bone loss from periodontal (gum) disease in mice, according to research led by scientists at the National Institute of Dental and Craniofacial Research (NIDCR), part of the National Institutes of Health. Drawing on animal and human data, the researchers found that buildup of the protein, called fibrin, triggers an overactive immune response that damages the gums and underlying bone.

The study, which was published in Science, suggests that suppressing abnormal fibrin activity could hold promise for preventing or treating periodontal disease, as well as other inflammatory disorders marked by fibrin buildup, including arthritis and multiple sclerosis.

Periodontal disease affects nearly half of Americans over age 30, and 70% of those 65 and older. It is a bacterial infection of the tissues supporting the teeth. In its early stages, periodontal disease causes redness and swelling (inflammation) of the gums. In advanced stages, called periodontitis, the underlying bone becomes damaged, leading to tooth loss. While scientists have known that periodontitis is driven in part by an exaggerated immune cell response, until now, it was unclear what triggered the response, and how it caused tissue and bone damage.

”Severe periodontal disease can lead to tooth loss and remains a barrier to productivity and quality of life for far too many Americans, especially those lacking adequate access to dental care,” said NIDCR Director Rena D’Souza, DDS, PhD. “By providing the most comprehensive picture yet of the underlying mechanisms of periodontal disease, this study brings us closer to more effective methods for prevention and treatment.”

At sites of injury or inflammation, fibrin normally plays a protective role, helping to form blood clots and activating immune cells to fight infection. But too much fibrin has been linked with health problems, including a rare form of periodontitis due to a condition called plasminogen (PLG) deficiency. In affected people, mutations in the PLG gene lead to fibrin buildup and disease at various body sites, including the mouth.

To explore the connection between abnormal fibrin buildup and periodontitis, the scientists, led by NIDCR investigators Niki Moutsopoulos, DDS, PhD, and Thomas Bugge, PhD, studied PLG deficiency in mice and analyzed human genetic data.

Like humans with the condition, PLG-deficient mice developed periodontitis, including periodontal bone loss and elevated levels of fibrin in the gums. The mice’s gums were crowded with immune cells called neutrophils, which are also found at high levels in common forms of periodontitis.

Neutrophils typically defend the oral cavity from harmful microbes. But an excessive neutrophil response is thought to cause tissue damage.

To find out if fibrin was driving this overactive response, the researchers impaired its ability to interact with (bind to) protein receptors on neutrophils. The weakened binding between fibrin and neutrophils completely prevented periodontal bone loss in PLG-deficient mice. Strikingly, it also reduced bone loss in normal mice with a common, age-related form of periodontitis, suggesting that similar mechanisms were at play in both forms of the disease.

“This study suggests that fibrin can cause neutrophil immunity to shift from protective to damaging in certain circumstances,” said Moutsopoulos, who credited postdoctoral fellow and study first author Lakmali Silva, PhD, for her research that led to the findings. “This fibrin-neutrophil engagement may be a driver of periodontitis.”

A genetic analysis of over 1,000 people seemed to support the animal findings. Even in the absence of PLG deficiency, variations in the PLG gene were linked to an increased risk of severe periodontitis, consistent with the idea that similar processes contribute to rare and common forms of the disease.

Taken together, the study suggests that excessive buildup of fibrin in the gums — whether due to changes in genes like PLG, chronic inflammation from a bacterial infection, or some combination of the two — triggers an elevated and ultimately harmful neutrophil response that causes periodontal disease.

“Our data support the idea that targeting the fibrin-neutrophil interaction could be a promising treatment avenue to explore in both rare and common forms of periodontitis,” added Silva.

References

Silva LM, et al. Fibrin is a critical regulator of neutrophil effector function at the oral mucosal barrier. Science. December 23, 2021. DOI: 10.1126/science.abl5450

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Enzyme Therapy Helps Rebuild Teeth

Study in Mice Suggests a New Approach to Treating Periodontal Disease

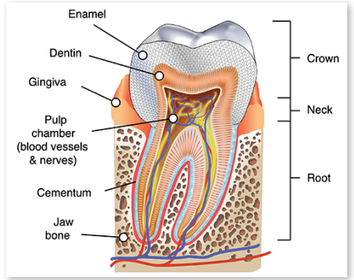
By Brandon Levy, Health Communications Specialist for the NIH’s Intramural Research Program

Our teeth are extremely tough, but neglectful oral hygiene practices and certain genetic disorders can still massively damage them. If this deterioration becomes bad enough, teeth can be permanently lost. In a recent study, IRP researchers identified a promising new strategy for helping the body regenerate a part of the tooth that is particularly difficult to repair.[1]

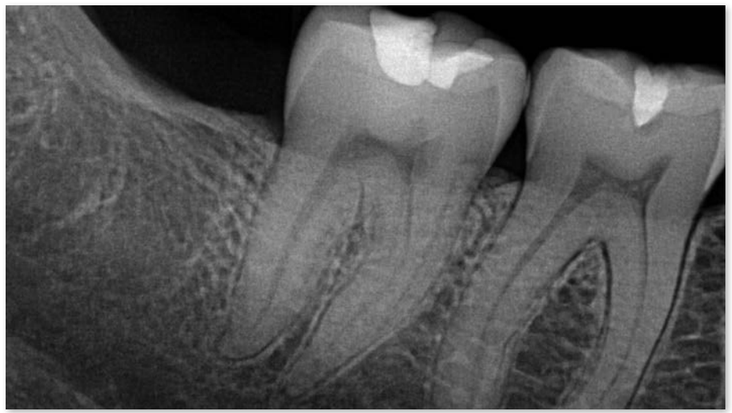
When it comes to taking care of our teeth, the enamel coating surrounding the upper portion of teeth tends to get most of the attention. It is, after all, the most visible part of our teeth and the hardest substance in the human body. However, a substance called cementum that surrounds the roots of our teeth is also incredibly important. The cementum helps our teeth remain in our mouths by attaching them to periodontal ligaments connected to surrounding jaw bone.

“The cementum around the tooth root is one of the tissues that has to be repaired to restore the tooth’s function after periodontal disease,” explains IRP senior investigator Martha J. Somerman, DDS, PhD, the new study’s senior author. “A lot of scientists have been focusing on promoting bone regrowth, but if you do that without considering the need for a healthy cementum, you will not restore proper function.”

Unfortunately, damaged cementum doesn’t regenerate very quickly when left to its own devices, if it heals at all, and current approaches to rebuilding it have not proven to be very effective. In the new study, Dr. Somerman’s team investigated whether an enzyme naturally found in the human body called alkaline phosphatase (ALP) could help repair damaged cementum by boosting the process that builds teeth and bone, known as mineralization. Prior research had shown that ALP transforms a chemical called pyrophosphate, which inhibits mineralization, into another molecule called phosphate, which promotes mineralization.



Human tooth diagram-en.svg from Wikimedia Commons by K. D. Schroeder, CC-BY-SA 4.0. The periodontal ligament (not labeled) connects the cementum to the jaw bone.



New IRP research suggests a novel strategy for treating periodontal disease, in which an infection of the gums causes the roots of the teeth to deteriorate, along with the parts of the jaw bone that support them. Image Courtesy of Schick by Sirona

The IRP study utilized a mouse model of periodontal disease that lacks the gene for an important bone- and cementum-building protein called bone sialoprotein. The researchers began by giving five-day-old mice a ‘systemic’ therapy that quadrupled their blood’s level of tissue-nonspecific alkaline phosphatase (TNAP), a form of ALP found in bones. At two months of age, the mice that recieved the therapy had cementum that was more than twice as thick as the cementum of their untreated counterparts, and they also showed greater growth of the jaw bone that surrounds the cementum. Moreover, their teeth were just as well-attached to the periodontal ligament as the teeth of untreated, genetically normal mice.

"Bone sialoprotein is thought to be a critical molecule for mineralization," Dr. Somerman explains, "so this is a perfect proof-of-principle model to examine whether you can regenerate cementum."

Next, using five-week-old mice with the same genetic defect, Dr. Somerman's team investigated the effects of delivering TNAP directly to the area where the degraded periodontal tissue was rather than raising TNAP levels in the entire body. The treated animals showed similar beneficial effects to the mice that had received the systemic TNAP-boosting therapy. What's more, the locally delivered TNAP treatment also promoted growth of the cementum and surrounding jaw bone in genetically normal mice.

A final set of experiments in cells showed that ALP corrected mineralization deficiencies in cementum-producing cells, called cementoblasts, that had the same genetic defect as the mice. However, treating those cells with a chemical that disrupts the transport of phosphate into cells diminished the ALP's beneficial effects, strongly suggesting that the TNAP treatment given to the mice promoted regeneration of the cementum and surrounding bone by increasing the amount of phosphate available for cementoblasts to use for the rebuilding process.

Moving forward, the IRP scientists will continue refining their TNAP treatment and working to move therapies based on their findings into clinical trials. The fact that TNAP is already FDA-approved for use in humans with genetic TNAP deficiencies could hasten its adoption as a treatment to help rebuild the cementum and jaw bone of people with severe periodontal disease. Importantly, delivering TNAP directly into the damaged area, as the researchers did in their new study, would likely have fewer side effects than introducing it throughout the body.

"We're incredibly excited about this," Dr. Somerman says. "Our studies showed that even in a normal mouse that doesn't have a genetic defect, you can promote the formation of cementum. It is very rewarding to identify factors, such as TNAP, as promising therapies for individuals with periodontal disease."

References:

1. Delivery of Alkaline Phosphatase Promotes Periodontal Regeneration in Mice. Nagasaki A, Nagasaki K, Kear BD, Tadesse WD, Thumbigere-Math V, Millán JL, Foster BL, Somerman MJ. J Dent Res. 2021 Apr 10; 220345211005677. doi: 10.1177/00220345211005677.

irp.nih.gov

About Martha J. Somerman, DDS, PhD

Martha J. Somerman, DDS, PhD, Director, National Institute of Dental and Craniofacial Research. Photo courtesy of NIH

Martha is the first woman to serve as Director of the National Institute of Dental and Craniofacial Research. Throughout her career, Martha has been a leader in defining factors that modulate formation of dental, oral, and craniofacial tissues, and applying that knowledge to designing evidence-based, predictable, targeted therapies to regenerate damaged or diseased tissue.

In 2016, Martha launched NIDCR 2030, which envisions a future where dental, oral, and craniofacial health and disease are understood in the context of the whole body.

Related to the NIDCR 2030 priorities, Martha spearheaded a new research focus on autotherapies — prevention and treatment tactics that will take advantage of the body's innate ability to repair and regenerate damaged or diseased tissues. Toward that end, she established the Dental, Oral, and Craniofacial Tissue Regenerative Consortium (DOCTR-C) to move basic research results more quickly into treatments. Martha is a vocal advocate for research synergy, the importance of public-private collaborations, and the essential need for clinicians to be partners in the scientific enterprise.

Throughout her career, Martha remained passionately committed to training the next generation of oral health researchers. In 2018, she launched the NIDCR Director's Postdoctoral Fellowship to Enhance Diversity in Dental, Oral, and Craniofacial Research. She was a pioneer in recognizing the need to support mid-career investigators when she initiated the NIDCR Award for Sustaining Outstanding Achievement in Research (SOAR) in 2017.

Report Details 20 Years of Advances and Challenges of Americans' Oral Health

Despite important advances in the understanding and treatment of oral diseases and conditions, many people in the U.S. still have chronic oral health problems and lack of access to care, according to a report by the National Institutes of Health. Oral Health in America: Advances and Challenges, is a follow-up to the seminal 2000 Oral Health in America: A Report of the Surgeon General. The new report, which is intended to provide a road map on how to improve the nation's oral health, draws primarily on information from public research and evidence-based practices and was compiled and reviewed by NIH's National Institute of Dental and Craniofacial Research (NIDCR) and a large, diverse, multi-disciplinary team of more than 400 experts.

The report updates the findings of the 2000 publication and highlights the national importance of oral health and its relationship to overall health. It also focuses on new scientific and technological knowledge — as well as innovations in health care delivery — that offer promising new directions for improving oral health care and creating greater equity in oral health across communities. Achieving that equity is an ongoing challenge for many who struggle to obtain dental insurance and access to affordable care.

"This is a very significant report," said NIH Acting Director Lawrence A. Tabak, DDS, PhD. "It is the most comprehensive assessment of oral health currently available in the United States and it shows, unequivocally, that oral health plays a central role in overall health. Yet millions of Americans still do not have access to routine and preventative oral care."

The newly issued report provides a comprehensive snapshot of oral health in America, including an examination of oral health across the lifespan and a look at the impact the issue has on communities and the economy. Major take-aways from the report include:

- Healthy behaviors can improve and maintain an individual's oral health, but these behaviors are also shaped by social and economic conditions.
- Oral and medical conditions often share common risk factors, and just as medical conditions and their treatments can influence oral health, so can oral conditions and their treatments affect other health issues.
- Substance misuse and mental health conditions negatively affect the oral health of many.
- Group disparities around oral health, identified 20 years ago, have not been adequately addressed, and greater efforts are needed to tackle both the social and commercial determinants that create these inequities and the systemic biases that perpetuate them.

"This is an in-depth review of the scientific knowledge surrounding oral health that has accumulated over the last two decades," said Rena D'Souza DDS, PhD, director of NIDCR, which oversaw and funded the project's three-year research program. "It provides an important window into how many societal factors intersect to create advantages and disadvantages with respect to oral health, and, critically, overall health."

The COVID-19 pandemic emerged while the report was being written. The science around SARS-CoV-2 continues to come into focus in real-time, and, although data were only starting to surface about the oral implications of the disease, the authors included a preliminary analysis of it to assess initial impacts.

The authors make several recommendations to improve oral health in America, which include the need for health care professionals to work together to provide integrated oral, medical, and behavioral health care in schools, community health centers, nursing homes, and medical care settings, as well as dental clinics.

They also identify the need to improve access to care by developing a more diverse oral health care workforce, addressing the rising cost of dental education, expanding insurance coverage, and improving the overall affordability of care.

"Although there are challenges ahead, the report gives us a starting point and some clear goals that offer reasons to be hopeful, despite those challenges," added D'Souza. "It imagines a future, as I do, in which systemic inequities that affect oral health and access to care are more fully addressed, and one in which dental and medical professionals work together to provide integrated care for all."

Scientists and public health professionals will use the report to identify areas of scientific inquiry and research as well as develop and implement programs that ultimately will improve the oral health of individuals, communities, and the nation.

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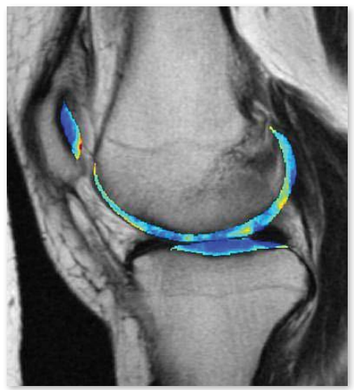
Machine Learning Detects Early Signs of Osteoarthritis

By Tianna Hicklin, PhD

A research team led by Dr. Shinjini Kundu of Carnegie Mellon University and the University of Pittsburgh and Dr.Gustavo Rohde of the University of Virginia investigated whether artificial intelligence could be used to analyze MRI images for early signs of osteoarthritis and predict who will develop the disease. They used MRI scans from 86 people who had no initial symptoms or visual signs of disease. About half the participants developed osteoarthritis after three years.

The study team included researchers from NIH's National Institute on Aging (NIA). It was also supported in part by NIH's National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of General Medical Sciences (NIGMS), and National Center for Advancing Translational Science (NCATS). Results were published on September 21, 2020, in the Proceedings of the National Academy of Sciences.

Osteoarthritis treatment usually begins with exercising and managing your weight. Photo courtesy of the NIH peakSTOCK / iStock / Getty Images Plus



The cartilage in this MRI scan of a knee is colorized to show greater contrast between shades of gray. Photo courtesy of NIH / Kundu et al., PNAS

The team used a technique they developed called three-dimensional transport-based morphometry (3D TBM) to identify biochemical changes, such as how much water is present, in cartilage using MRI scans. Using 3D TBM, they analyzed baseline "cartilage maps" of the participants' knees. After three years, they compared the cartilage maps for the participants who were eventually diagnosed with osteoarthritis with those who were not.

Using machine-learning algorithms, the team trained the system to automatically differentiate between people who would progress to osteoarthritis and those who wouldn't. The technique detected specific biochemical changes in the center of the knee's cartilage of those who were pre-symptomatic at the time of the baseline imaging, including decreases in water concentration. The system accurately detected 78% of future osteoarthritis cases.

"The gold standard for diagnosing arthritis is X-ray. As the cartilage deteriorates, the space between the bones decreases," says study co-author Dr. Kenneth Urish of the University of Pittsburgh. "The problem is, when you see arthritis on X-rays, the damage has already been done."

More studies are needed to determine whether 3D TBM could be useful as a clinical tool to predict who may develop osteoarthritis and benefit from early interventions.

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NIH, DC Government Form Partnership to Reduce Sleep-related Infant Deaths

Three-year partnership will develop D.C. project for infant safe sleep education and outreach.

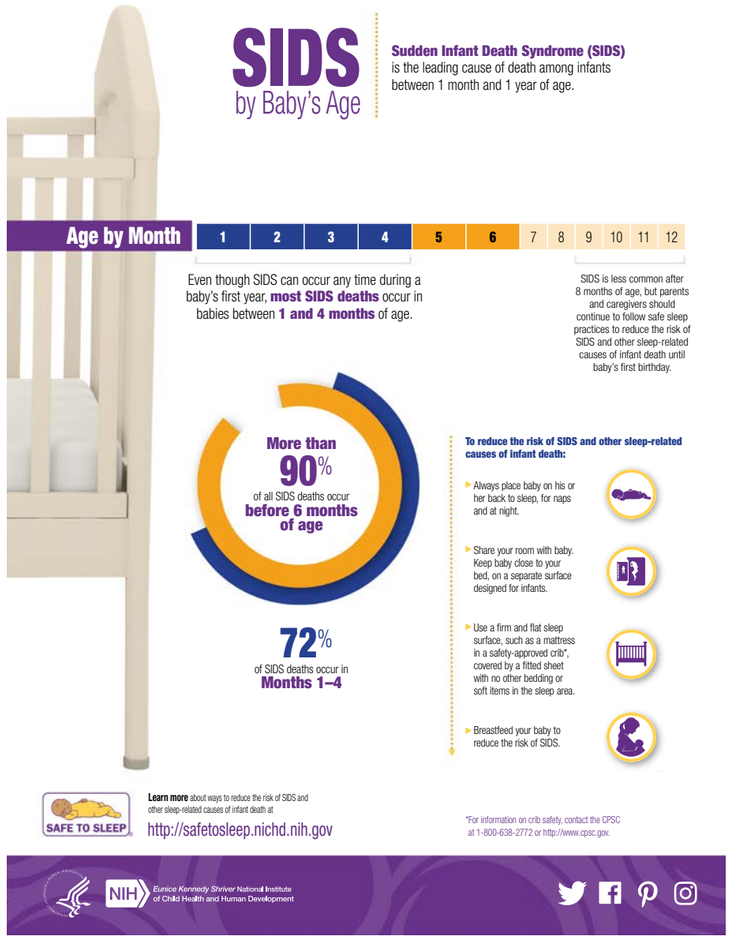
The National Institutes of Health and the District of Columbia government are teaming up to raise awareness among District parents and caregivers about how to reduce the risk of sudden infant death syndrome (SIDS) and other sleep-related causes of infant death, such as accidental suffocation.

Although many U.S. states and territories have seen decreases in sleep-related infant deaths over the last few years, the District's Office of the Chief Medical Examiner reported an increase in these deaths between 2014 and 2018. Sleep-related causes of death include SIDS — the sudden, unexplained death of an infant younger than 1 year of age that does not have a known cause, even after a full investigation — or suffocation, overlay, or other deaths from an unsafe sleep environment.

The Safe to Sleep campaign, led by the NIH's Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), will work with the District of Columbia Office of the Chief Medical Examiner, the Thrive by Five DC initiative and other D.C. groups to understand information or service gaps related to safe infant sleep and determine how those gaps contribute to deaths and risks for families in the District. The collaboration, known as the D.C. Safe Sleep Education and Outreach Project, will then develop and implement the outreach and awareness campaign to inform D.C. parents and caregivers about how they can bridge these gaps.

"By combining science with safe sleep practices and tailoring safe sleep messages and activities to area parents and caregivers, this new collaboration has the potential to save infant lives," said Diana W. Bianchi, MD, NICHD Director. "We are excited to work with our colleagues in the District of Columbia government and other local groups to help babies and families thrive."

Photo courtesy of the NIH



"Every parent or caregiver wants their child to have the best start in life," said Dr. Francisco J. Diaz, Chief Medical Examiner for the District. "The D.C. Safe Sleep Education and Outreach Project will provide families with valuable information on how to provide the safest possible sleeping environment for their infants, helping to reduce sleep-related deaths in the District and providing opportunities for each child to have a strong start."

"I am excited about this collaboration and the partnerships it is sparking to move us toward sustainable solutions and more positive outcomes for our babies. Together with families, we can make sure our babies have everything they need to thrive, and that includes safe sleep environments and practices," said Dr. Faith Gibson Hubbard, Executive Director of Thrive by Five.

NICHD and collaborators, including the American Academy of Pediatrics (AAP) and the Centers for Disease Control and Prevention (CDC), launched the Safe to Sleep® campaign as the Back to Sleep campaign in 1994 to raise awareness among caregivers and healthcare providers about ways to reduce the risk of SIDS. The collaborators expanded the campaign to Safe to Sleep® in 2012 to focus on reducing risks for other sleep-related causes of infant death, such as suffocation.

The campaign translates safe infant sleep recommendations from the AAP into messages, educational resources, and outreach materials for lay and provider audiences. Key messages include always placing infants on their backs to sleep, using a firm and flat sleep surface such as a mattress in a safety-approved crib, and breastfeeding.

Recent research findings jointly published by NICHD, CDC, and the Health Resources and Services Administration suggest that other safe sleep behaviors, such as keeping loose bedding and soft objects out of baby's sleep area and room sharing with parents instead of bed sharing are not as well known. As a result, parents and caregivers may unknowingly be creating an unsafe sleep environment and putting their babies at risk.

With guidance and technical support from NICHD, the Office of the Chief Medical Examiner, Thrive by Five DC and other partners will assess the District's existing infant mortality data and safe sleep education and resources to determine if additional support systems or communications are needed to ensure that parents and caregivers make optimal choices related to safe infant sleep. Through focus groups and online surveys, they will identify any barriers to safe sleep practices among area residents and develop interventions to address those barriers. They will also identify and test safe sleep messages and materials, emphasizing the needs of and feedback from communities with the highest number of infant sleep-related deaths.

After testing is complete, these messages will provide the basis for the campaign, which will be a comprehensive outreach effort that will include community events, local media and community faith leaders, public service announcements, and media outreach. Dr. Diaz's office notes that the D.C.-focused project will likely launch in late 2021.

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High Dose of Concentrated Therapy Produces Several Lasting Benefits for Children with Cerebral Palsy

Findings on Constraint-Induced Movement Therapy may inform updates to clinical practice guidelines.

By Theresa Hayes Cruz, PhD, Director of NICHD's National Center for Medical Rehabilitation Research

Children with hemiparetic cerebral palsy, a movement disorder that affects use of one side of the body, showed improved use of the arm and hand after receiving a high dose of Constraint-Induced Movement Therapy (CIMT) in a clinical trial funded by the National Institutes of Health.

The study, published in Pediatrics, suggests that the more intensive level of CIMT—3-hour sessions, five days a week for four weeks — produced the most noticeable and longer lasting improvements. A moderate dose — 2.5-hour sessions, three days a week for four weeks—did not produce gains significantly greater than the control group, which received a standard combination of physical and occupational therapy.

CIMT involves restricting the better functioning arm and hand with a splint or cast while a highly trained therapist engages the child in activities that reinforce and shape the movement and functional skills in the impaired arm and hand.

While CIMT is widely accepted as more effective than conventional forms of physical and occupational therapy, little was known about effects of different doses of CIMT or whether constraints should be used only during the sessions or continuously throughout treatment. NIH's Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) funded a randomized, controlled clinical study — the Children with Hemiparesis Arm and Hand Movement Project, or CHAMP — to compare variations of CIMT against conventional forms of therapy.

Photo courtesy of NIH, AaronAmat/Getty Images/iStockphoto

The study included 118 children ages 2 to 8 years old with hemiparetic cerebral palsy. Children were randomly assigned to one of four treatment groups — 30 or 60 total hours of CIMT combined with either a splint or a cast — or to the control group.

Children who received the high-dose of 60 hours of CIMT using either constraint had the greatest improvements on a variety of upper extremity skills, such as grasping, moving, manipulating objects and self-care activities, as evaluated by trained assessors at the end of treatment and six months later.

However, the research team noted that children in the control group also improved more than expected. The authors think this may have resulted from a higher-than-normal dose of conventional therapy, lasting four-to-five hours per week. More research is needed to evaluate these differences and long-term benefits of CIMT.

The study was led by Sharon Landesman Ramey, PhD, of Virginia Tech's Fralin Biomedical Research Institute and included colleagues from the University of Virginia, Ohio State University and Nationwide Children's Hospital.

Article:

Ramey SL, DeLuca SC, Stevenson RD, Conaway M, Darragh AR, and Lo W. Constraint-induced movement therapy for cerebral palsy: A randomized trial. Pediatrics DOI: https://doi.org/10.1542/peds.2020-033878 (2021)

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Parenting Program to Prevent Obesity in Firstborn Children Benefits Siblings

NIH-funded study results show potential long-term value of childhood obesity prevention strategy.

An intervention shown to help first-time parents prevent childhood obesity has found spillover effects in second-born children as well, even without further training for the parents. The results are from a study funded by the National Institute of Diabetes and Digestive and Kidney Diseases, part of the National Institutes of Health. The intervention, called responsive parenting, teaches parents how to interact constructively with their infant during feeding, bedtime, and play. Responsive parenting may be an important childhood obesity prevention strategy for families and an effective way to promote healthy growth in children. The study, called SIBSIGHT, was published Dec. 21 in Obesity.

SIBSIGHT followed a responsive parenting intervention with first-time parents, called Intervention Nurses Start Infants Growing on Health Trajectories (INSIGHT). INSIGHT was a randomized controlled trial designed to reduce unhealthy, rapid weight gain in infancy to prevent obesity in childhood. INSIGHT found that, after completing the three-year study, children in the responsive parenting group had a body mass index (BMI) in a healthier range compared to those in the control group and significantly lower rates of overweight or obesity in the responsive parenting compared to control group.

INSIGHT is now the first educational intervention for obesity prevention of first children to demonstrate spillover effect to future children. In the United States, more than 13% of children(link is external) aged 2-5 have obesity, a number that rises as children age. "SIBSIGHT findings are promising because the education gets to parents at optimal times, in the first months of life and now even before a subsequent pregnancy," said Dr. Voula Osganian, NIDDK program director for pediatric clinical obesity. "SIBSIGHT demonstrates the potential long-term value of this childhood obesity prevention strategy."

In the observational SIBSIGHT study, 117 firstborn infants that participated in INSIGHT and their siblings were monitored for one year. The first and second children whose parents received the responsive parenting intervention had a statistically significant difference in BMI compared to children in the control group, with BMI being 0.44 and 0.36 units lower respectively or about a 2.5% difference in weight. "The continuing benefit of responsive parenting training is remarkable because parents of second children received no INSIGHT responsive parenting booster messaging in the observation-only evaluation," said Dr. Jennifer S. Williams, lead author and director of the Center for Childhood Obesity Research at the Pennsylvania State University in University Park.

Photo courtesy of NIH and Yuganov Konstantin/Shutterstock

First-time parents assigned to the responsive parenting group during the INSIGHT study were educated on how to respond to their infant's needs across four behaviors: feeding, sleep, interactive play, and emotional regulation. This group also learned such strategies as how to put infants to bed drowsy, but awake, and avoid feeding infants to sleep; anticipate and respond to infants waking up at night; when to introduce solid foods; how to use growth charts; and how to limit sedentary time. The control group received a home safety intervention. Both groups received four home visits from a research nurse during infancy, followed by three annual research center visits.

"The vast majority of parents have multiple children, and so a parenting strategy that can be taught once and then show benefits through subsequent children may be a path forward in helping curb the rising problem of childhood obesity," Osganian said.

At 12 months of age, the benefit in second children was similar to that observed in first children. Researchers conclude that the INSIGHT training prevented the use of nonresponsive feeding practices and helped establish consistent feeding routines in second siblings. "A child's first months are a critical period for parents and health care providers to intervene and promote healthy behaviors and growth, and the INSIGHT and SIBSIGHT results show us a potential way do this effectively," said NIDDK Director Dr. Griffin P. Rodgers. "Early and long-term obesity prevention strategies help set up our children for a healthy future."

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NIH Study Shows Hyaluronan is Effective in Treating Chronic Lung Disease

Naturally produced by the body, hyaluronan represents a new class of biologic that significantly improves lung health in patients with severe COPD

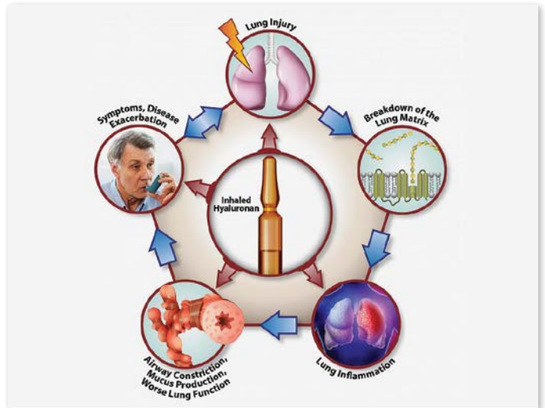
Researchers at the National Institutes of Health and their collaborators found that inhaling unfragmented hyaluronan improves lung function in patients suffering from severe exacerbation of chronic obstructive pulmonary disease (COPD). Hyaluronan, a sugar secreted by living tissue that acts as a scaffold for cells, is also used in cosmetics as a skin moisturizer and as a nasal spray to moisturize lung airways. Utilized as a treatment, hyaluronan shortened the amount of time COPD patients in intensive care needed breathing support, decreased their number of days in the hospital, and saved money by reducing their hospital stay.

The study, published online in Respiratory Research, is a good example of how examining the impacts of environmental pollution on the lungs can lead to viable treatments. Several years ago, co-senior author Stavros Garantziotis, MD, medical director of the Clinical Research Unit at the National Institute of Environmental Health Sciences (NIEHS), part of NIH, showed that exposure to pollution causes hyaluronan in the lungs to break down into smaller fragments. These fragments irritate lung tissue and activate the immune system, leading to constriction and inflammation of the airways. He determined that inhalation of healthy, unfragmented hyaluronan reduces inflammation by outcompeting the smaller hyaluronan fragments.

Garantziotis offered an analogy for how the inflammation occurs. He said hyaluronan surrounds cells like mortar surrounds bricks. Introducing pollution causes cracks in the mortar, breaking it into smaller chunks. "These smaller chunks irritate the body and activate the immune system, leading to inflammation," Garantziotis said. "Reintroducing the full-length hyaluronan, like a fresh coat of mortar, means it is less irritating and reduces the amount of inflammation."

Since hyaluronan was approved in Italy for airway moisturization, Garantziotis worked with colleagues in Rome to see if inhalation of full-size hyaluronan could improve lung function in critically ill COPD patients. He explained that the patients were using a breathing apparatus similar to a continuous positive airway pressure (CPAP) machine to treat their acute exacerbation of COPD. This apparatus provided breathing support by blowing air into the airways through a mask.

"Inhaled hyaluronan qualifies as a stimulating aid for patients with exacerbated COPD, as it is safe and easy to administer," said co-senior author Raffaele Incalzi, MD, Department of Medicine,



Research shows that inhaling hyaluronan interferes at almost every step of the COPD cycle, making it a potent treatment for chronic lung disease. Photo courtesy of Stavros Garantziotis, MD.

Campus Bio-Medico University and Teaching Hospital, Rome. "Furthermore, it acts locally, only in the bronchial tree, and, thus, cannot interfere with any systemic drug."

Garantziotis also wanted to know what was producing airway constriction in the lungs of COPD patients. He theorized that thick mucus may be involved. Collaborating with scientists at the University of Alabama at Birmingham (UAB), they grew airway cells from emphysema patients in culture and looked at how mucus moved in the cells. They saw that mucus flowed more easily after administering hyaluronan.

Co-author Steven Rowe, MD, director of the Gregory Fleming James Cystic Fibrosis Research Center at UAB, said if patients with severe COPD took hyaluronan, the treatment would improve mucus transport and aid their recovery.

Current treatments for lung disease include inhaled steroids, antibiotics, and bronchodilators, so using a molecule that is already found in the body is a new concept. The goal now for Garantziotis is to study this treatment in more patients in the U.S., so he can understand the optimal conditions and dosing that will produce the most benefit.

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Lung Development May Explain Why Some Non-smokers Get COPD and Some Heavy Smokers Do Not

According to a new study, people with small airways relative to the size of their lungs may have a lower breathing capacity and, consequently, an increased risk for COPD — even if they don't smoke or have any other risk factors. The study, funded in part by the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health, will publish in the June 9 issue of JAMA.

Researchers have long puzzled over why nearly a third of cases occur in people who never smoked. Now they may finally have an answer — and it may be linked to how lungs develop in certain people.

"This work, stemming from the careful analysis of lung images of COPD patients, shows that an abnormal lung development may account for a large proportion of COPD risk among older adults," said James Kiley, Ph.D., director of NHLBI's Division of Lung Diseases. "More research is needed to understand what drives this occurrence and to devise possible interventions."

COPD, the fourth leading cause of death in the United States, causes airflow blockage and breathing-related problems that can severely limit a person's day-to-day activities. Smoking, asthma, or air pollution account for many COPD cases, but up to 30% of cases occur in people who never smoked, and only a minority of heavy smokers develop the disease, suggesting that there are other risk factors at play.

Previous research offered a clue about a possible cause, finding that about half of older adults with COPD appeared to have low lung function early in life. Benjamin Smith, M.D., a pulmonary physician in the Department of Medicine at Columbia University Irving Medical Center, New York City, who was involved in the new study, explained the phenomenon.

When people breathe, they move air through their airways, beginning with the windpipe or trachea, which branches out to smaller airways called bronchi and bronchioles. As people grow, their airways are thought to develop in proportion to their lungs, but in some people, the airways grow smaller or larger than expected — a condition called dysanapsis — for reasons that are not clear.

To find out if small airways might be the culprit for COPD in people who did not smoke or have other risk factors, a team led by Smith looked at records for more than 6,500 older adults participating in three studies that included smokers and nonsmokers with and without COPD. Each study — the Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study, the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS), and the Canadian Cohort of Obstructive Lung Disease (CanCOLD) study — assessed dysanapsis using computed tomography (CT) scans of the lungs.

The MESA Lung study, based in six U.S. cities, included white, African American, Hispanic, and Chinese American people who were age 69 on average. The participants from the CanCOLD study were age 67 on average and came from nine Canadian cities. SPIROMICS, based at 12 U.S. medical centers, included people who were age 63 on average and reported 20 or more pack-years of smoking.

In the MESA Lung and CanCOLD studies, participants with smaller airways relative to lung size were much more likely to develop COPD compared with those with the larger airways relative to lung size. The association remained after considering standard COPD risk factors, including smoking, pollutants, and asthma.

The researchers then focused on participants from the CanCOLD study who never smoked and heavy smokers from the SPIROMICS study. Never smokers with COPD had much smaller airways relative to lung size, whereas the heavy smokers who did not have COPD had larger than normal airways.

"These results show that small airways relative to lung size are a very strong risk factor for COPD," said Smith, the lead study author. "This helps us to understand why 30% of COPD can occur in people who never smoked." With normal aging, lung function declines, so people who already have low lung function to begin with may develop COPD later in life, even if they don't smoke, he explained.

Smith added that the findings may also help explain why some lifelong heavy smokers do not develop COPD. People with larger airways relative to lung size may be able to withstand lung damage from smoking and still have enough breathing reserve to prevent them from developing COPD. Still, given the multiple health problems caused by tobacco, Smith emphasized that smokers should do their best to quit.

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Amping Up Our Investment in Autoimmune Disease Research

By Lindsey A. Criswell, MD, MPH, DSc, NIH Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases

The National Institutes of Health, the Foundation for the National Institutes of Health (FNIH), eight pharmaceutical companies and five non-profit organizations have partnered to further our understanding of the cellular and molecular disease pathways in autoimmune and immune-mediated diseases. The Accelerating Medicines Partnership® Autoimmune and Immune-Mediated Diseases (AMP® AIM) program will advance the discovery of disease mechanisms and therapeutic targets in rheumatoid arthritis, lupus, psoriasis, psoriatic arthritis, and Sjögren's disease.

We know that many autoimmune diseases share common inflammatory pathways and clinical features, and often respond to treatment similarly. Many of these diseases result in persistent damage to multiple tissues and organ systems, and have a major impact on health, well-being, and quality of life. Using a collaborative approach, AMP AIM will define the shared and unique immune mechanisms in these disorders, which will enable the development of new and effective therapies for people with autoimmune diseases.

AMP AIM builds on the research infrastructure, datasets and novel technologies of our prior AMP investment in rheumatoid arthritis and lupus. This new initiative provides an extraordinary opportunity to further advance the identification of specific drug targets in these and other autoimmune diseases.

A key feature of the AMP AIM program is its commitment to patient engagement. It will incorporate strategies to include patient input and will emphasize the importance of patient-reported outcomes. Nonprofit supporters include the Arthritis Foundation, the Lupus Foundation of America, the Lupus Research Alliance, the National Psoriasis Foundation, and the Sjögren's Foundation, all of which are members of the NIAMS Coalition, as well.

Lindsey A. Criswell, MD, MPH, DSc. Photo courtesy of the National Institute of Arthritis and Musculoskeletal and Skin Diseases

In addition to NIAMS and our valued NIAMS Coalition partners, AMP AIM is supported by the National Institute of Allergy and Infectious Diseases, the National Institute of Dental and Craniofacial Research, and the NIH Office of Research on Women's Health. Private funding partners beyond those listed above include AbbVie, Bristol Myers Squibb, GlaxoSmithKline plc (GSK), Janssen Research & Development, LLC, Novartis Pharma AG, Pfizer Inc., Sanofi, and UCB. The partnership is managed by the FNIH.

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About Dr. Criswell

Lindsey A. Criswell, MD, MPH, DSc, became the director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) in February, 2021.

Prior to joining NIAMS, Dr. Criswell was vice chancellor of research at the University of California, San Francisco (UCSF). A board-certified rheumatologist, Dr. Criswell was also a professor of rheumatology and a professor of orofacial sciences at UCSF.

She has a bachelor's degree in genetics and a master's degree in public health from the University of California, Berkeley, and an MD from UCSF. She earned a DSc in genetic epidemiology from the Netherlands Institute for Health Sciences, Rotterdam. She completed a residency in internal medicine and a fellowship in rheumatology.

As NIAMS director, Dr. Criswell oversees the Institute's annual budget of nearly $625 million, which supports research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases. The Institute seeks to advance health through biomedical and behavioral research as well as through research training and dissemination of information on research progress in these diseases.

Between 1994 and the time she became NIAMS director, Criswell was a principal investigator on multiple NIH grants and published more than 250 peer-reviewed journal papers. Her research focused on the genetics and epidemiology of human autoimmune disease, particularly rheumatoid arthritis and systemic lupus erythematosus. Using genome-wide association and other genetic studies, her research team contributed to the identification of more than 30 genes linked to these disorders.

In 2021, Criswell was elected to the Association of American Physicians, an honor extended to physicians with outstanding credentials in biomedical research. Criswell's other honors include the Kenneth H. Fye, MD, endowed chair in rheumatology and the Jean S. Engleman distinguished professorship in rheumatology at UCSF, and the Henry Kunkel Young Investigator Award from the American College of Rheumatology. She also was named UCSF's 2014 Resident Clinical and Translational Research Mentor of the Year. While at UCSF, she mentored some four dozen students (high school through medical/graduate school), medical residents, postdoctoral fellows and junior faculty.

New Clues to the Causes of Lupus

By Kirstie Saltsman, PhD

Insights from two recent studies suggest novel avenues for treating the autoimmune disease systemic lupus erythematosus (SLE). The NIH's National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supported the pair of studies that sought to better understand why the immune system mistakenly attacks its own tissues and organs, as happens in SLE. The work could possibly impact other autoimmune diseases as well.

SLE is a chronic, inflammatory illness, that most often strikes women of childbearing age, though men and children also may be affected. The symptoms vary but the most common are sore, swollen joints, muscle aches and fatigue. Over time, the disease can damage the body's organs and cause serious problems like kidney or cardiovascular disease. SLE has no cure, but non-steroidal anti-inflammatory medicines, steroids and other immune suppressants help control the symptoms. Many research efforts aim to understand how the immune system goes awry in SLE, with the goal of uncovering better ways to treat it.

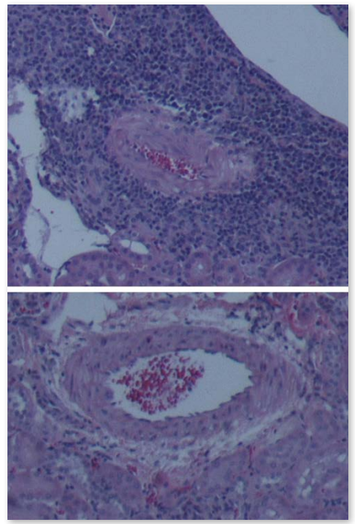
Betty Diamond, MD, of the Feinstein Institute for Medical Research, led one such effort that produced results in Nature Immunology. Dr. Diamond's group, intrigued by an earlier finding that a variation in a gene called PRDM1 increases a person's risk of developing SLE, delved into the gene's role in the immune system. Building on this work, Diamond's team showed that female mice — but not males — engineered to lack PRDM1 in dendritic cells, a type of immune cell, showed signs of autoimmunity problems similar to those in people with SLE.

Additional experiments showed that loss of PRDM1 in dendritic cells leads to a rise in an enzyme, cathepsin S, which breaks up proteins in preparation for the fragments' display on the cell surface. This processing step is an essential part of the T cell-mediated arm of the immune response, an important contributor to autoimmunity. When the researchers treated the engineered mice with a cathepsin S inhibitor, the lupus-like features abated in the female mice. While further research is needed, this finding suggests that cathepsin S represents a novel therapeutic target for SLE.

"What we'd like to be able to do is to intervene early in lupus, before any tissue damage occurs," said Dr. Diamond. "By studying SLE risk genes, we hope to gain a better understanding of the immune system changes that set the stage for the disease and ultimately to find ways to stymie it before it truly sets in."

The second study, published in the Journal of Immunology and led by Vasileios Kyttaris, MD, of the Beth Israel Deaconess Medical Center, focused on an inflammatory molecule called IL-23. His group noticed that this molecule is elevated in the blood of SLE patients, suggesting a role in the disease. To investigate this possibility, the researchers tested the effect of IL-23 on cultured T cells taken from SLE patients. They found that exposure to IL-23 led to the expansion of the troublesome T cell subtypes associated with SLE.

Probing further, they next tested IL-23's effects in a mouse model of SLE. These mice, called MLR.lpr mice, spontaneously exhibit signs of lupus, including high levels of T cell subtypes associated with the disease and acute kidney damage. To see if IL-23 plays a part in the mice's SLE-like symptoms, they engineered a strain of MLR.lpr mice that is insensitive to IL-23's effects. They observed lower levels of SLE-associated T cell subtypes and inflammatory molecules in these mice, as well as reduced severity of kidney damage, compared to IL-23-sensitive MLR.lpr mice.



Kidney blood vessels (red) in a mouse model of lupus show signs of damage, as evidenced by immune cells (dark purple/light pink) collecting around them [upper panel]. This effect is eliminated in IL-23-insensitive mice [lower panel]. Photo credit Vasileios Kyttaris, MD, Beth Israel Deaconess Medical Center.

These findings revealed that IL-23 likely plays an important role in SLE, and showed that in mice, blocking the molecule's effects diminishes signs of the disease. Additional research will reveal if the same is true in humans.

"Lupus, a disease that affects more than a million Americans, is treated with non-specific medicines that can have troubling side effects," said Dr. Kyttaris. "The discovery that we can prevent disease development, especially kidney damage, in lupus-prone animals by targeting IL-23 offers the possibility of a new, more targeted approach toward treatment."

Dr. Diamond's study was supported by NIAMS (R01-AR065209), the Lupus Research Alliance and the Defense Threat Reduction Agency.

Dr. Kyttaris's study was supported by NIAMS (R01-AR060849) and National Institute of Allergy and Infectious Diseases (R01-AI085567).

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Symptoms of lupus also differ from person to person. For example, one woman with lupus may have swollen knees and fever. Another woman may be tired all the time or have kidney trouble. Someone else may have rashes. Over time, new symptoms can develop or some symptoms may happen less often. Photo courtesy of The Office on Women's Health

It is estimated that 1.5 million Americans have lupus, more women than men, most commonly in women ages 15 to 44, or during the years they can have children.

There are several different types of lupus:

- Systemic lupus erythematosus (SLE) is the most common and most serious type of lupus. SLE affects all parts of the body. Common symptoms include fatigue, hair loss, sun sensitivity, painful and swollen joints, unexplained fever, skin rashes, and kidney problems.
- Cutaneous lupus erythematosus (CLE) is a skin disease that can affect people with or without SLE. Symptoms may include rashes, hair loss, swelling of the blood vessels, ulcers, and sun sensitivity.
- Drug-induced lupus is caused by certain medicines. The symptoms of drug-induced lupus are like those of SLE, such as joint pain, muscle pain, and fever. But symptoms are usually not as serious. Also, drug-induced lupus rarely affects major organs. Most often, the disease goes away when the medicine is stopped. The medicines that most commonly cause drug-induced lupus are used to treat other chronic health problems. These include seizures, high blood pressure, or rheumatoid arthritis. But not everyone who takes these medicines will get drug-induced lupus.
- Neonatal lupus is a rare condition in infants that is caused by certain antibodies from the mother. These antibodies can be found in mothers who have lupus. But, if you have lupus, this does not mean you will definitely pass it to your baby. Most infants of mothers with lupus are healthy. It is also possible for an infant to have neonatal lupus even though the mother does not have lupus currently. But, if a baby is born with lupus, often the mother will develop lupus later in life. At birth, an infant with neonatal lupus may have a skin rash, liver problems, or low blood cell counts. These symptoms often go away completely after several months and have no lasting effects. Infants with neonatal lupus also can have a rare but serious heart defect.

Studies have found an increase in bone loss and fracture in individuals with SLE. Individuals with lupus are at increased risk for osteoporosis for many reasons. To begin with, the glucocorticoid medications often prescribed to treat SLE can trigger significant bone loss. In addition, pain and fatigue caused by the disease can result in inactivity, further increasing osteoporosis risk. Studies also show that bone loss in lupus may occur as a direct result of the disease. Of concern is the fact that 90 percent of the people affected with lupus are women, a group already at increased risk for osteoporosis.

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Casting the NET Wide: How Neutrophils Shape Chronic Autoimmune and Inflammatory Diseases

Mariana Kaplan Is Discovering New Ways to Fight Lupus

By Natalie Hagen, NCATS

Known as the "disease with a thousand faces," systemic lupus erythematosus is a lifelong autoimmune disease with a wide range of symptoms and signs — fatigue, fever, joint pain, facial rash and skin lesions, shortness of breath, and more. It may develop suddenly or slowly and be mild or severe, with people affected going through periods of flare up and remission of their symptoms. Lupus affects mostly women of childbearing age and causes widespread inflammation, damage to organ systems, and premature cardiovascular disease.

Lupus is thought to be caused by an overactive immune system in which autoantibodies attack a body's own cells, tissues, and organs. Normal antibodies attack antigens produced by foreign substances such as bacteria, viruses, or toxins. Autoantibodies, on the other hand, attack autoantigens produced by the body itself.

Previously, it was believed that white blood cells called lymphocytes were the predominant drivers of this disease. Recent discoveries and technical advances, however, have suggested that neutrophils — another type of white blood cell — may also play an important role in immune dysregulation.

NIH Senior Investigator Mariana Kaplan is exploring how neutrophils wreak havoc on the immune system in lupus and other autoimmune disorders. Her interest in immunology was piqued when, as a medical student at the National Autonomous University of Mexico's School of Medicine (Mexico City), she began seeing patients with lupus. "The idea that someone's body starts attacking itself rather than the outside environment — I thought that was a really fascinating problem," said Kaplan, who is chief of the Systemic Autoimmunity Branch in the National Institute of Arthritis and Musculoskeletal and Skin Diseases and is also involved in lupus clinical trials in the NIH Clinical Center.

Kaplan has identified several mechanisms, including a role for neutrophils, associated with the development and prevention of premature atherosclerosis in people with lupus. She presented her research on neutrophils and their role in autoimmunity on June 9, 2021, at the annual G. Burroughs Mider Lecture, which is part of the Wednesday Afternoon Lecture Series (WALS).

Neutrophils undergo a process called NETosis: The neutrophils extrude nuclear material bound to cytoplasmic proteins in a meshwork called neutrophil extracellular traps (NETs) that can then capture and kill pathogens. Kaplan determined that this process also causes the neutrophils to release autoantigens — such as host DNA and histones and other proteins.

A subset of proinflammatory neutrophils from patients with lupus, compared with those from patients without, are more likely to form NETs with a greater potential for developing an immune response. The result is increased inflammation and enhanced vascular damage.

There are also differences in how male and female immune systems work. Females have a stronger immune response than males, which may explain why women tend to react better to vaccines and infections. However, that enhanced immune response also makes females predisposed to inflammatory and autoimmune diseases such as lupus. Kaplan has found that sex hormones modulate neutrophil metabolism: Female neutrophils are significantly more active than male ones and have an enhanced ability to form NETs and respond to inflammatory insults. In one experiment, she showed that when male neutrophils are treated with the female sex hormone estradiol, they acquire the bioenergetic profile and behavior of female neutrophils. This finding could have important implications in the context of why women are more likely to get lupus. (Proc Natl Acad Sci U S A 117:16481—16491, 2020)

Current treatments for lupus that suppress numerous immune cells and inflammatory cytokines can have serious side effects. Kaplan's findings have implications for the development of new individualized, sex-specific therapies that target neutrophils. Furthermore, strategies that suppress the aberrant NET formation seen in lupus — without hampering other important antimicrobial functions — could prove a useful approach for autoimmune and chronic inflammatory diseases that involve neutrophil dysregulation.

"While in some patients, lymphocytes may be the main players in lupus, there may be other patients [in whom] neutrophils are playing a very important role," she said. "So if you treat these patients the same way, you're probably not going to get the same therapeutic response."

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Researchers Uncover Clues to Why Some Wounds Don't Heal

Innovative research made possible by prestigious NIH Bench-to-Bedside and Back Program Award

By Stephanie Mathews, PhD

Unlike acute wounds, such as a paper cut or scraped knee, chronic wounds can take months to heal and leave a person at greater risk for developing infection, chronic pain, and other problems. Slow-healing foot ulcers, a complication of diabetes, are a common type of chronic wound.

Diabetic foot ulcers can greatly impact a person's quality of life and put them at risk for limb amputations or early death. Treating diabetic foot ulcers represents a significant challenge to doctors and costs billions of dollars annually in the U.S.

In a new study published in Nature Communications, researchers identify defects in the wound healing process that might explain why such wounds heal slower or not at all. The scientists also pinpoint a critical step in the pathway, the series of events contributing to wound repair, that might be a good target for developing new treatments for diabetic foot ulcers.

The collaboration included groups led by two established skin biologists. Maria Morasso, PhD, is chief of the Laboratory of Skin Biology at the National Institute of Arthritis and Musculoskeletal and Skin Diseases. She is an expert in skin barrier formation and function and has contributed to our understanding of rapid wound healing. Marjana Tomic-Canic, PhD, is a professor of dermatology and director of the Wound Healing and Regenerative Research Program at the University of Miami. She is a leader in chronic, non-healing wound research.

The new paper underscores the power of scientific collaboration. Morasso and Tomic-Canic brought multi-disciplinary teams together under one mission—to heal patients. First, the scientists analyzed human tissue samples to identify the molecular culprits responsible for delayed healing. Then they confirmed their findings using specialized laboratory mice. The long-term goal of the work is to find ways to improve chronic wound healing in humans.

This collaborative research was made possible by an NIH Bench-to-Bedside and Back Program (BtB) Award. The NIH BtB Program was established in 1999 to encourage collaboration between NIH's intramural researchers and their colleagues at institutions around the country. The goal of the program is to translate basic scientific findings into real-world treatments for patients.

Marjana Tomic-Canic PhD. Photo courtesy of NIH

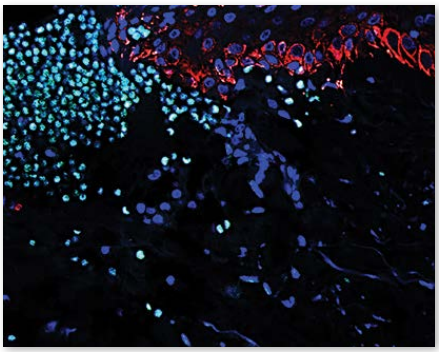
Chronic Wounds Struggle to Heal

Wound healing is a normal process that involves four tightly controlled stages. The second stage, the inflammatory phase, is thought to be the engine that drives the process. During this stage, white blood cells gather at the wound. These cells fight off infection and recruit other immune cells that promote tissue repair.

Chronic wounds heal very slowly because they do not advance through all the phases. Instead, chronic wounds seem to get stuck. They are unable to get past the inflammatory stage. This can lead to additional complications, such as wound infections, or even limb amputations.

Maria Irene Morasso, PhD. Photo courtesy of NIH

Scientists don't fully understand why chronic wounds halt at this stage, so it has been difficult to design effective treatments. As evidence, current treatment options for diabetic foot ulcers are



Representative image of human skin wound showing neutrophil (teal) recruitment to promote a proper inflammatory response during healing. Photo credit: Andrew Sawaya, PhD, Laboratory of Skin Biology, NIAMS

very limited and no new therapies have been developed in the past 20 years.

The researchers started their investigation of chronic wounds in a body part where wounds heal very quickly — the mouth. Think about the last time you bit your cheek while eating. You probably experienced sharp pain as your teeth pierced the tissue, but the wound healed within a few days.

Previous research from the Morasso group uncovered factors that allow mouth wounds to heal rapidly. This knowledge of rapid wound healing has markedly advanced the understanding of delayed chronic wound healing.

Lack of FOXM1 is Key to Delayed Healing

The scientists sought to uncover what goes wrong in chronic wound healing by studying three different types of healing: injuries in the mouth (fast healing), skin injuries (average healing), and diabetic foot ulcers (slow healing). Morasso, Tomic-Canic, and their collaborators collected human tissue samples for each of these three types of injury.

Then they used a common gene sequencing technique to take a close look at the molecules involved in wound healing. Collectively, these molecules — specific genes and the proteins that control them — are known as a transcriptional network.

This strategy led to some interesting discoveries that could explain why chronic wounds heal slowly. Right away, the team noticed transcriptional networks that control white blood cell movement and survival were revved up in mouth and skin tissues. Particularly striking was that the tissues were flooded with specialized white blood cells called neutrophils and macrophages, which are essential to wound healing.

A very different picture was revealed in diabetic foot ulcers: transcriptional networks were weakly activated, and neutrophils and macrophages were absent from the tissue. Diabetic foot ulcers are unable to accumulate these critical white blood cells, which might partially explain why these wounds are slow to heal.

So, what causes white blood cell recruitment to go awry in diabetic foot ulcers? The scientists used computer-based software to scan through transcriptional networks to find a possible key. The analysis pinpointed the FOXM1 protein. FOXM1 is a regulator that triggers the recruitment of white blood cells.

Sure enough, when the scientists examined levels of FOXM1 in the three types of tissue, they found that FOXM1 was suppressed in diabetic foot ulcers but strongly activated in mouth and skin wounds. If scientists could somehow increase FOXM1 in diabetic foot wounds, they might be a step closer to a treatment for these hard-to-heal wounds.

Although the research seems promising, it was done in isolated human skin tissues, which don't replicate the complexity of a living organism. To confirm the role of FOXM1 in a living system, the scientists turned their attention to wounded diabetic mice. Diabetic mice are a well-established animal model for studying diabetes.

One group of wounded diabetic mice received a chemical to block FOXM1 activity, mimicking the FOXM1-deficient environment found in diabetic foot ulcers. A second group of wounded diabetic mice did not receive the FOXM1-blocking chemical and served as a control.

If FOXM1 is necessary for proper healing, then blocking its activity should slow the healing process. Indeed, mice treated with the FOXM1 blocker experienced reduced recruitment of immune cells and slower healing compared to the untreated mice. These results confirmed that FOXM1 is essential for the healing of wounds, and that, without it, healing is delayed.

Future Directions

Morasso and Tomic-Canic uncovered important clues that explain why chronic wounds are slow to heal. Their collaborative research on diabetic foot ulcers, a common type of chronic wound, revealed that the absence of FOXM1 led to insufficient recruitment of specialized white blood cells and delayed healing.

Failure to accumulate the specialized cells is a likely reason why diabetic foot ulcers, like other chronic wounds, cannot get past the inflammatory phase. The results suggest that finding a way to boost the activity of FOXM1 might lead to a treatment for diabetic foot ulcers, and possibly other chronic wounds.

Morasso and Tomic-Canic agree that this study is a launching pad for multiple approaches. Going forward, the researchers aim to further their understanding of the molecular underpinnings of the disease, analyze clinical outcomes, and eventually translate their discoveries into new therapies for diabetic foot ulcers.

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